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Stereochemistry of a Rearrangement of B and C Rings in Clovane Skeleton

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Abstract: The isocaryolane structure **6** has been assigned to a minor product of the TCNE-catalysed cyclization of caryophyllene 4α,5β-oxide (**3**). A Wagner-Meerwein rearrangement of rings B and C of the clovane skeleton (**1**) has been explored by deuterium labelling of 9α-bromo-2β-methoxyclovane (**4a**). © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Compounds with the clovane skeleton (**1**) are formed from trans-caryophyllene (**2**) and caryophyllene oxide (**3**) by acid catalyzed cyclization.[1] Under superacid conditions, compounds with the clovane skeleton yield derivatives which have undergone further rearrangement in ring A [2] rather than rings B and C.

2β-Methoxyclovan-9α-ol (**4**) was obtained as the main product from the solvolytic cyclization of caryophyllen-4β,5α-oxide (**3**) using tetracyanoethylene (TCNE) as a mild catalyst.[3] Compound **4** is an inhibitor of the growth [4] of the plant pathogen, *Botrytis cinerea*, an organism that causes serious losses of commercial crops. There is a structural similarity between this inhibitor and the sesquiterpenoid botrylane phytotoxic metabolites produced by *B. cinerea*.[5] In order to examine the scope of this structural similarity, we required some rearranged clovanes. To our knowledge, no rearrangements of the B and C rings of the clovane skeleton have been reported.

Since clovanes with an ether function at C-2 do not readily undergo further reactions on ring A, we have been able to explore the rearrangement reactions of rings B and C of compound **4** and their stereochemistry.

RESULTS AND DISCUSSION

2β-Methoxyclovan-9α-ol (**4**) was obtained from caryophyllen-4β,5α-oxide (**3**) by treatment with TCNE.[3] The reaction conditions were modified in order to improve the yield of compound **4**. A careful examination of

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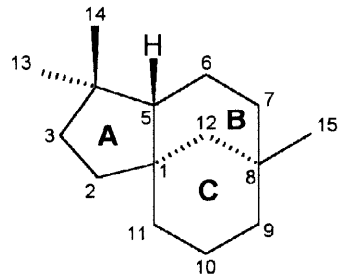
the reaction mixture led to the detection of two previously unreported minor compounds: 8β-methoxy-caryophyll-3(4)-en-5α-ol (**5**) and isocaryolan-9-one (**6**).



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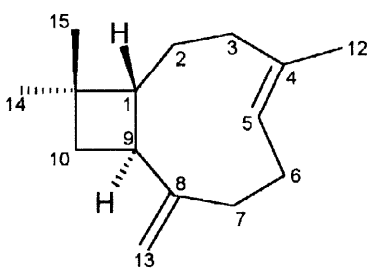

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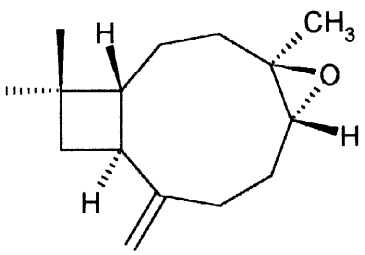

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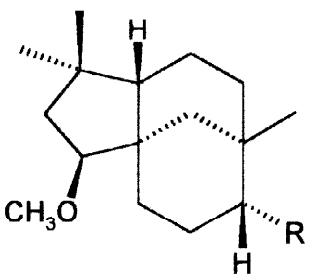
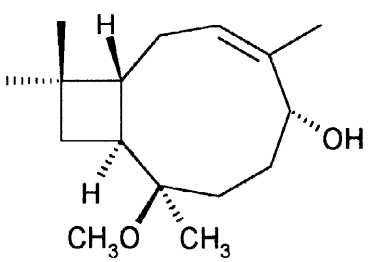


4 R = OH
4a R = Br
4b R = OCOH



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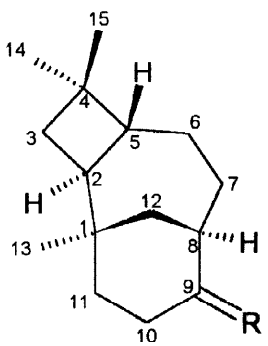
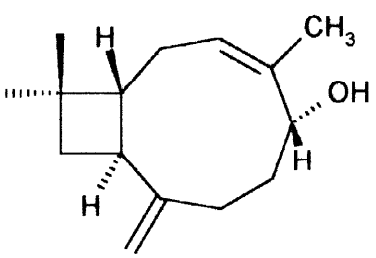


6 R = O
6a R = β-H; α-OH



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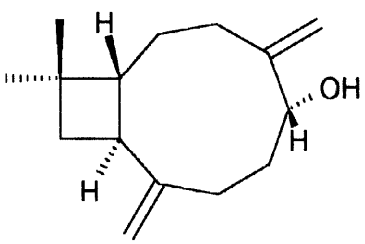

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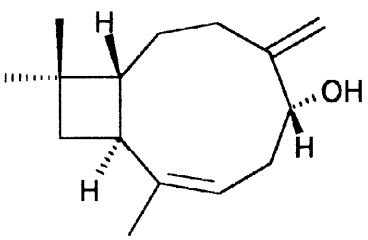

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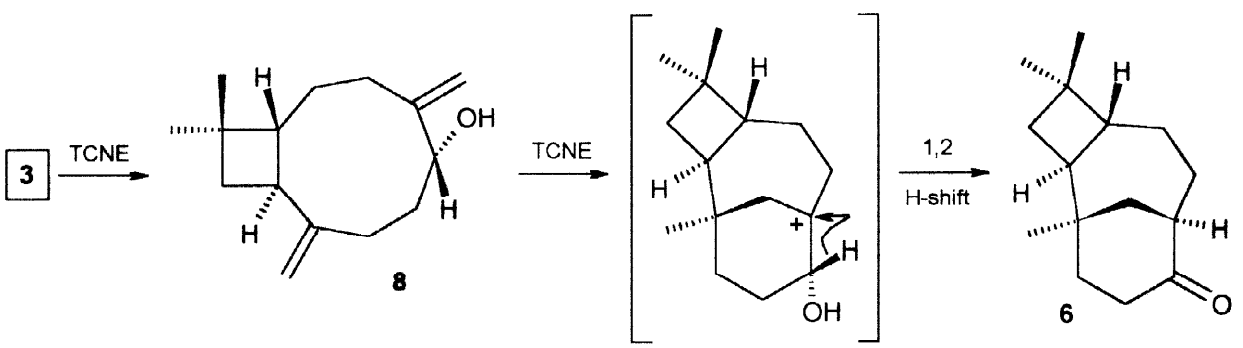
Isocaryolan-9-one (**6**) was also detected as a minor product when caryophyllene oxide (**3**) was treated with TCNE in DMSO. The main products were the allylic alcohols 7 and **8**. When the fraction containing both allylic alcohols 7 and **8** was treated with TCNE and DMSO, the ketone **6** , and allylic alcohols 7 and **9** were obtained, but none of the exocyclic allylic alcohol **8** was detected.

The structures of the minor products were established by spectroscopic analysis. The ^{1}H-NMR spectrum of the alcohol **5** possessed signals at δ_H 5.4 ppm (dd, 1H, J 9.9 and 9.3 Hz, C<u>H</u>=C), δ_H 4.32 ppm (brd, 1H, J 7.5 Hz, C<u>H</u>OH) , δ_H 3.09 ppm (s, OC<u>H</u>$_3$) and δ_H 1.78 ppm (s, 3H, C<u>H</u>$_3$), assigned to H-3, H-5β, β-OMe and H-12, respectively. Comparison with the spectra of other compounds with the caryophyllene skeleton[6] together with

nuclear Overhauser enhancement and 2D COSY NMR studies led to a full assignment of the ^{1}H-NMR. The significant n.O.e. enhancements are shown in figure 1 and are fully consistent with the stereochemistry. Compound **6** showed absorption at 1704 cm^{-1} in its IR spectrum and a resonance at δ^{13}_C 215.7 ppm (s) in its ^{13}C-NMR spectrum consistent with a ketone. Many of the signals in the ^{1}H-NMR spectrum were overlapped preventing a full assignment and deduction of the structure. Treatment of compound **6** with $LiAlH_4$ in an inert atmosphere, gave the crystalline alcohol **6a**, the structure and stereochemistry of which were established by X-ray crystallography (see figure 2). This in turn served to establish the stereochemistry of the starting ketone (**6**). Although compounds with the isocaryolane skeleton have been obtained from caryophyllene oxide (**3**)[7], the 1,2 hydride shift (see scheme 1) which leads to the formation of the ketone **6** had not been observed previously in this series.



Scheme 1

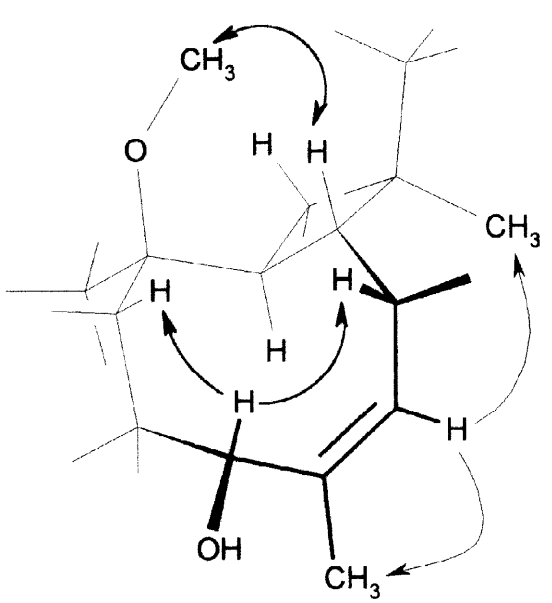


Figure 1. Selected n.O.e. correlations observed in **5**

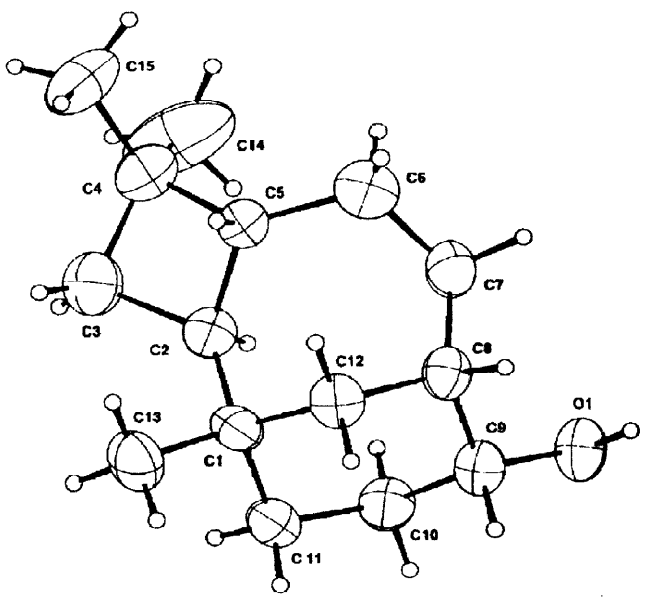
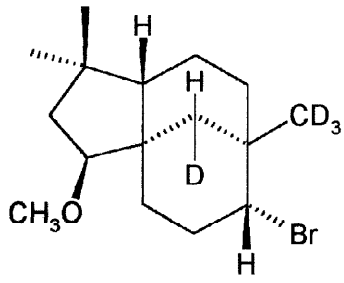


Figure 2. ORTEP drawing of **6a**

Carefully purified 2β-methoxyclovan-9α-ol (**4**) was treated with hydrogen bromide in acetone. Under these conditions we recovered the starting material (**4**) and 2β-methoxy-9α-bromoclovane (**4a**). The stereochemistry of compound **4a** was established by a n.O.e study (see figure 3). A careful study of the reaction mixture did not reveal any of the epimeric 9β-bromo compound. The retention of the stereochemistry at C-9 in compound **4a** can only be explained in terms of a double Wagner-Meerwein rearrangement involving the β-face of C-8 and C-9. A similar result was observed when compound **4** was treated with HCOONa in HCOOH, yielding compound **4b**, which has a H-9β stereochemistry.



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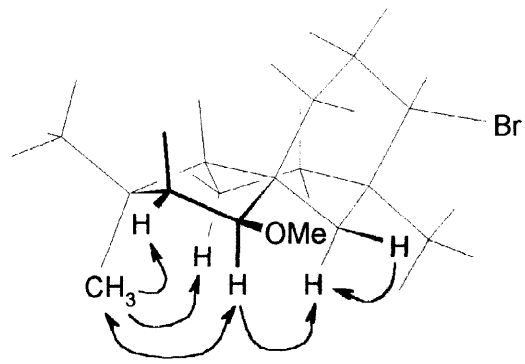
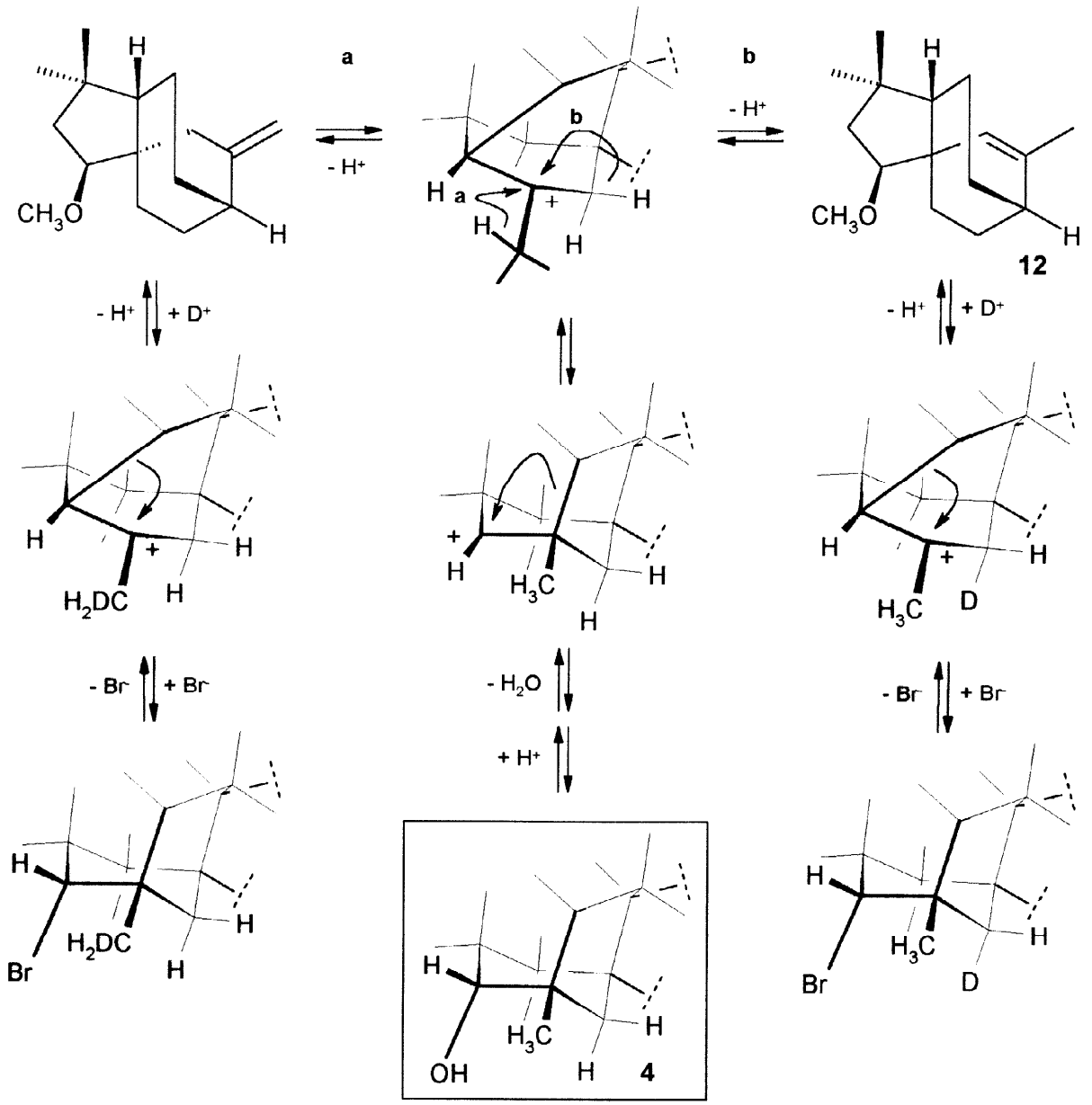


Figure 3 Selected n.O.e. correlations observed in **4a**.

In order to clarify the behaviour of rings B and C in the clovane series under these conditions, compound **4** was treated under identical conditions with deuterium bromide in deuterioacetone. A careful NMR spectroscopic and mass spectrometric analysis of the product showed that it was 12[^{2}H],15[^{2}H$_3$]-9α-bromo-2β-methoxyclovane (**10**). High resolution mass spectrometry showed molecular ions at 318.1847-320.1499 m/z corresponding to $C_{16}H_{23}O^2H_4{}^{79}Br$ (^{81}Br). The ^{1}H-NMR spectrum of compound **10** showed several significant differences. Resonances at δ_H 1.77 ppm (H-12α) and δ_H 1.06 ppm (H-15) had disappeared whilst the resonance at δ_H 1.00 ppm (H-12β) had collapsed from a doublet to a singlet. The ^{2}H-NMR spectrum of compound **10** showed two resonances at δ^2_H 1.75 ppm (s, ^{2}H-12α) and δ^2_H 1.01 ppm (s, ^{2}H-15) in the ratio 1:3 confirming the deuterium incorporation.

The retention of configuration at C-9 and the incorporation of deuterium can be explained by scheme 2. This unusual rearrangement which parallels that found in rings C and D of the tetracyclic diterpenes, has not been detected previously in clovane chemistry.

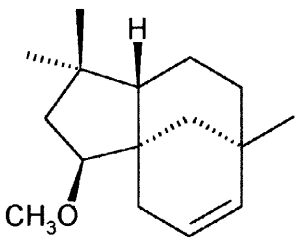
A further facet of this rearrangement was observed when compound **4** was treated with diethyl azodicarboxylate (DEAD) and triphenylphosphine in toluene (80°C) for several hours. Two olefinic products, 2β-methoxyclov-9(10)-ene (**11**) and 1R,5S,9R-4,4-dimethyl-8-methylenetricyclo-[6.3.2.0^{1,5}]-dodecane (**12**) were obtained.



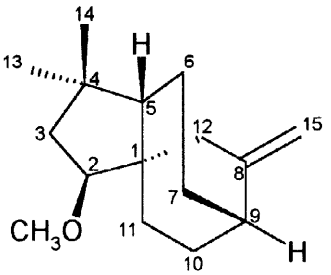
Scheme 2

The major product (**11**) was identified by comparison of its ^{1}H-NMR spectrum with those of compounds **4** and **4a**. The ^{1}H-NMR spectrum showed alkene proton resonances at δ_H 5.70 ppm (ddd, 1H, J 2.5, 4.7 and 9.8 Hz) and δ_H 5.22 ppm (dd, 1H, J 1.5 and 9.8 Hz), a methoxyl signal at δ_H 3.25 ppm (3H, s) and the H-2α resonance at δ_H 3.14 ppm (1H,t, J 3.5 Hz). These data are consistent with the structure **11** for the clovane skeleton compound. Compound **12** showed signals in its ^{1}H-NMR assigned to an exocyclic methylene, δ_H 4.71 ppm (1H,dd, J 2.3 and 4.3 Hz) and 4.65 ppm (1H,dd, J 2.1 and 4.3 Hz), a methoxyl signal at δ_H 3.32 ppm (3H, s) and the H-2α resonance at δ_H 3.28 ppm (1H,dd, J 6.0 and 10.5 Hz) (both from ring A). There were

only two methyl group signals in the ^{1}H-NMR spectrum [δ_H 0.96 and 0.78]. This data is consistent with the structure (**12**) for the rearranged product.



11



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EXPERIMENTAL

Melting points were measured with a Reichert-Jung Kofler block and are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Perkin-Elmer 881 spectrophotometer. ^{1}H and ^{13}C NMR measurements were obtained on Varian Gemini 200 and Varian Unity 400 NMR spectrometers with $SiMe_4$ as internal reference. Mass spectra were recorded on VG 12-250 spectrometer at 70 eV: HPLC was performed with a Hitachi/Merck L-6270 apparatus equiped with a UV-VIS detector (L 4250) and a differential refractometer detector (RI-71). TLC was performed on Merck Kiesegel 60 F_{254}, 0.2 mm thick. Silica gel (Merck) was used for column chromatography. Purification by HPLC was accomplished using a Si gel column (Hibar 60, 7 μm, 1 cm wide, 25 cm long).

Procedure for the methanolysis of 3 with TCNE. Caryophyllene oxide (200 mg) dissolved in methanol (1ml), was treated with TCNE (11.6 mg) and stirred for 24 hours at room temperature. The progress of the reaction was monitored by TLC. When the epoxide was consumed (24 hr.) the solvent was evaporated under vacuum. The resulting gum was redissolved in a volatile solvent (AcOEt), washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded a crude product that was purified by column chromatography on silica gel, with increasing gradients of ethyl acetate in petroleum ether. The readily separable products were 2β-methoxyclovan-9α-ol (**4**) (96 mg, 42%),[3] 5α-hydroxycaryophylla-3,8(13)-diene (40 mg, 20%) (**7**),[3] 4β-methoxycaryophyll-8(13)-en-5α-ol (13 mg, 6%),[3] 8β-methoxy-5α-hydroxycaryophylla-3 (4)-ene (**5**) (7 mg, 3%), and isocaryolan-9-one (**6**) (22 mg, 11%).

8β-Methoxy-5α-hydroxycaryophylla-3(4)-ene (5). White crystals, mp 129-132 °C. $[\alpha]^{25}_D$ -8.4 (c= 10.5 mg/ml, $CHCl_3$). IR (film) 3241, 2935, 2864, 2362, 1664, 1468 , 1356, 1227, 1140, 1085, 1063, 1008,

857, 725 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ_H 0.98 (s, 3H, H-13α), 1.02 (s, 3H, H-14α), 1.11 (s, 3H, H-15β), 1.33 (ddd, 1H, J= 3.2 Hz, J= 5.7 Hz, $J_{7\beta\text{-}7\alpha}$= 15.1 Hz, H-7β), 1.56 (d, 2H, J= 9.3 Hz, H-10), 1.69 (m, 1H, $J_{6\text{-}6'}$= 13.1 Hz, H-6′), 1.76 (m, 1H, H-1), 1.78 (s, 3H, H-12), 1.90 (m, 1H, H-6), 1.97 (td, 1H, J= 3.5 Hz, $J_{7\alpha\text{-}7\beta}$= 15.1 Hz, H-7α), 2.03 (m, 1H, H-2α), 2.15 (m, 1H, H-2β), 2.30 (ddd, 1H, J= 9.9 Hz, J= 9.3 Hz, H-9), 3.09 (s, 3H, O-$C\underline{H}_3$), 4.32 (da, 1H, J= 7.5 Hz, H-5β), 5.4 (t, 1H, J= 8.3 Hz, H-3). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ^{13}_C 19.2 (q, C-12), 19.6 (q, C-15), 23.9 (q, C-14), 26.3 (t, C-2), 29.7 (q, C-7), 30.3 (q, C-13), 34.0 (s, C-11), 34.1 (t, C-8*), 34.9 (t, C-6*), 40.4 (d, C-9), 40.4 (d, C-1), 49.2 (q, O-$\underline{C}H_3$), 73.4 (d, C-5), 124.6 (d, C-3). EIMS ***m/z*** (70 eV) 252 (2) [M]$^+$, 237 (2)[M^+-15], 220 (7), 202 (15), 167 (16), 164 (37), 162 (17), 159 (12), 149 (31), 147 (17), 146 (31), 138 (24), 137 (14), 121 (32), 111 (35), 109 (38), 107 (40), 106 (71), 105 (61), 95 (57), 94 (51), 85 (100). HREIMS 252.2073 ($C_{16}H_{28}O_2$ requires 252.2089).

Isocaryolan-9-one (6). Oil. $[\alpha]^{25}_D$ -13.3 (c= 2.93 mg/ml, $CHCl_3$). IR (film): 2952, 2865, 1704, 1456, 1367, 1111 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ_H 0.88 (s, 3H, H-13β), 0.88 (s, 3H, H-14α), 0.96 (s, 3H, H-15), 1.16 (dddd, J= 3.8, 5.6, 1.3, 1.3 Hz, H-7), 1.33 (ddt, J= 5.2, 13.1, 12.9 Hz, H-6α), 1.48-1.43 (m, 1H, *H-11β, H-6β), 1.47 (dd, 1H, J= 10.0, 10.3 Hz, H-11β), 1.55 (dd, 1H, J= 10.2, 7.7 Hz, H-3α), 1.72 (dd, 1H, J= 2.5, 14.0 Hz, H-12α), 2.03 (dd, 1H, J= 9.6, 14.0 Hz, H-12β), 2.27 (m, 1H, H-7), 2.52-2.39 (m, 3H, H-8, H-10 and H-10′), (* interchangeable signals). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ^{13}_C 22.0 (q, C-14), 25.8 (t, C-6), 26.2 (q, C-13), 30.0 (t, C-7), 30.7 (q, C-15), 31.9 (s, C-1), 33.1 (s, C-4), 36.0 (t, C-10), 36,8 (tt, C-3 and C-12), 42.2 (td, C-11 and C-2), 45.0 (d, C-8), 46.4 (d, C-5), 215.7 (s, C-9). EIMS m/z (70 eV) 220 (26) $[M]^+$, 205 (4) [M^+ -OCH_3], 177 (15) [M^+ -CH_3-CO], 169 (100), 146 (68). HREIMS 220.1843 ($C_{15}H_{24}O$ requires 220.1827).

Reduction of isocaryolan-9-one (6) with $LiAlH_4$. Isocaryolan-9-one (**6**) (100 mg) was dissolved in dry diethyl ether and $LiAlH_4$ (8 mg) was added and the reaction mixture was stirred for 12 hours under an inert atmosphere. When isocaryolan-9-one was consumed (TLC control), H_2O (10 ml) was slowly added and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The mixture was redissolved in CH_2Cl_2 and purified by column chromatography on silica gel, with increasing gradients of ethyl acetate in petroleum ether, giving compound **6a** (79 mg, 80 %).

Isocaryolan-9α-ol (6a). White crystals mp: 129-132 °C. $[\alpha]^{25}_D$ + 27.1 (c= 16.4 mg/ml, $CHCl_3$). IR (film) 3293, 2923, 2852, 1685, 1461, 1055 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ_H 0.74 (s. 3H, H-13), 0.97 (s, 3H, H-15β), 0.98 (s, 3H, H-14α), 1.05 (dd, 1H, J= 4.6, 13.9 Hz, H-12′), 1.20 (ddd, 1H, J= 4.3, 9.0, 13.2 Hz, H-11′), 1.24 (dd, 1H, J= 10.6, 10.6 Hz, H-3′), 1.43-1.34 (m, 3H, H-7′, H-6′ and H-11), 1.46 (dd, 1H, J= 7.9, 10.6 Hz, H-3), 1.55 (m, 1H, H-6), 1.86-1.63 (m, 5H, H-10, H-10′, H-5, H-12 and H-7), 2.12-2.04 (m, 2H, *H-8, H-2), 2.09 (m, 2H, H-2 ,H-5), 3.71 (ddd, J= 11.2, 5.6, 5.6 Hz, H-9β), (* interchangeable signals). ^{13}C-NMR

($CDCl_3$, 50 MHz) $\delta^{13}C$ 20.6 (q, C-14), 24.2 (t, C-6), 24.3 (t, C-7), 26.4 (q, C-13), 27.9 (t, C-10), 30.6 (q, C-15), 31.4 (s, C-1*), 34.3 (s, C-4*), 36.0 (t, C-3), 38.3 (d, C-2), 38.4 (t, C-11), 39.5 (d, C-8), 40.2 (t, C-12), 46.1 (d, C-5), 73.1 (d, C-9). EIMS *m/z* (70 eV) 222 (10) $[M]^+$, 205 (11) $[M^+ -OH]$, 204 (65) $[M^* -H_2O]$, 148 (77), 133 (64), 107 (69), 93 (100). HREIMS 222.2002 ($C_{15}H_{26}O$ requires 222.1984). X- Ray crystal data and structure refinement are given in table 1.

Treatment of caryophyllene oxide (3) with TCNE in DMSO. Caryophyllene oxide (**3**) (442 mg) dissolved in DMSO (14 ml), was treated with TCNE (30 mg) and stirred for 4 days at room temperature. The progress of the reaction was monitored by TLC. When the epoxide was consumed, the mixture was diluted with ethyl acetate (50 ml) and washed with 2 x 50 ml of brine and the solvent was dried over Na_2SO_4. Evaporation of the solvent afforded a crude reaction product that was purified by column chromatography on silica gel with increasing gradients of ethyl acetate in petroleum ether, giving compounds **7** [3] (205 mg, 46%), **8** [3] (85 mg, 19%) and **6** (10 mg, 2%).

Treatment of a mixture of allyllic alcohols 7 and 8 with TCNE in DMSO. A mixture of 205 mg of **7** and 85 mg of **8**, dissolved in DMSO (10 ml), was treated with TCNE (30 mg) and stirred for 1 month. Then, the mixture was diluted with ethyl acetate (50 ml) and washed with 2 x 50 ml of brine and the solvent was dried over Na_2SO_4 . Evaporation of the solvent afforded a crude reaction product that was purified by column chromatography on silica gel with increasing gradients of ethyl acetate in petroleum ether, giving compounds **7** [3] (38 mg), **9** [3] (32 mg) and **6** (42 mg).

Treatment of 2β-methoxyclovane-9α-ol (4) with HBr in acetone. 2β-Methoxyclovan-9α-ol (**4**) (300 mg), dissolved in acetone (60 ml), was treated with HBr (47%) (60 mg) and stirred for 2 hours at room temperature. Water was added and the reaction mixture was neutralized with anhydrous sodium carbonate. The resulting gum was extracted with ethyl acetate and dried over anhydrous Na_2SO_4 . The solvent was evaporated under vacuum and the crude reaction product was purified by column chromatography on silica gel with increasing gradients of ethyl acetate in petroleum ether to afford 9α-bromo-2β-methoxyclovane (**4a**) (60%) and starting material.

9α-Bromo-2β-methoxyclovane (4a). Oil. $[\alpha]^{25}_D$ -12.3 (c=10 mg/ml, $CHCl_3$). IR (fim): 3433, 2947, 2867, 1465 , 1205 , 1110. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ_H 0.85 (s, 3H, H-13α), 1.02 (s, 3H, H-14β), 1.02 (d, 1H, H-12β), 1.06 (s, 3H, H-15),1.12(m, 1H, H-11β), 1.3-1.25 (m, 2H, H-6α and H-7β), 1.43-1.34 (m, 2H, H-5 and H-6β), 1.59-1.49 (dd, 1H, $J_{3\beta-3\alpha}$=11.9 Hz, H-3β), 1.54 (m, 1H, H-7α), 1.72 (dd, 1H, $J_{3\alpha-2\alpha}$=5.6, $J_{3\alpha-3\beta}$=11.9 Hz, H-3α), 1.77 (d, 1H, $J_{12\beta-12\alpha}$=12.7 Hz, H-12α), 1.88 (dd, 1H, J=4.4 Hz, $J_{11\alpha-11\beta}$= 13.3 Hz, H-11α), 1.97 (m, 1H, $J_{10\alpha-10\beta}$=14.3 Hz, H-10α), 2.24 (dddd, 1H, $J_{10\beta-10\alpha}$= 14.3 Hz, H-10β), 3.34 (dd, 1H, $J_{2\alpha-3\alpha}$= 5.6

Hz, $J_{2\alpha\text{-}3\beta}$=10.5 Hz, H-2α), 3.39 (s, 3H, CH_3O), 4.17 (br s, 1H, H-9β). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ^{13}_C 20.4 (t, C-6), 25.3 (q, C-13), 27.0 (t, C-11), 28.7 (t, C-10), 31.1 (q, C-14), 32.5(q, C-15), 33.6 (t, C-7), 35.8 (s, C-8), 37.0 (s, C-4), 37.2 (t, C-12), 44.3 (s, C-1), 44.3 (t, C-3), 52.0 (d, C-5), 58.3 (q, O-CH_3), 68.1 (d, C-9), 89.8 (d, C-2). EIMS *m/z* (70 eV) 316 (0.5) $[M]^+$, 286 (0.6) $[M\text{-}CH_3OH]^+$, 269 (1), 235 (3) $[M\text{-}Br]^+$, 203 (8), 147 (13), 99 (100). HREIMS 314.1260-316.1205 ($C_{16}H_{27}OBr$ requires 314.1245-316.1226).

Formolysis of 2β-methoxyclovan-9α-ol (4).[8] A solution of sodium formate in formic acid was prepared by dissolving 2.5 g of sodium carbonate in 125 ml of formic acid. 2β-Methoxyclovan-9α-ol (**4**) (80 mg) was added and the reaction mixture was heated under reflux for 4 hours. Once the reaction was completed (TLC control), water was added and reaction mixture was neutralized with anhydrous sodium carbonate. The resulting gum was extracted with ethyl acetate and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude reaction product was purified by column chromatography on silica gel with increasing gradients of ethyl acetate in petroleum ether to afford 9α-formyloxy-2β-methoxyclovane (**4b**) (36 mg, 40%).

9α-Formyloxy- 2β-methoxyclovane (4b). Oil. IR (film) 3424, 2930, 1726, 1465, 1186 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) ^{1}H-NMR ($CDCl_3$, 400 MHz) δ_H 0.85 (s, 3H, H-13α), 0.87 (s, 3H, H-15), 0.95 (d, 1H, J=9.1 Hz, H-12), 1.02 (s, 3H, H-14β), 1.09 (m, 1H, H-11β), 3.33 (dd, 1H, J= 5.6, 10.2 Hz, H-2α), 3.35 (s, 3H, C<u>H</u>$_3$O), 4.66 (br s, 1H, H-9β), 8.09 (brs, 1H, C<u>H</u>O). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ^{13}_C 20.4 (t, C-6), 23.5 (t, C-11), 25.3 (q, C-13), 27.1 (t, C-10), 28.1 (q, C-14), 31.2 (q, C-15), 32.7 (t, C-7), 33.6 (s, C-8), 37.1 (s, C-4), 37.3 (t, C-12), 42.1 (s, C-1), 43.9 (t, C-3), 50.6 (d, C-5), 58.2 (q, O-<u>C</u>H$_3$), 77.2 (d, C-9), 89.8 (d, C-2), 213.1 (s,C=O). EIMS *m/z* (70 eV) 280 (3) $[M]^+$, 265 (15) $[M\text{-}15]^+$, 248 (10) $[M\text{-}CH_3OH]^+$, 234 (8) $[M\text{-}HCOOH]^+$, 202 (20) $[M\text{-}CH_3OH\text{-}HCOOH]^+$, 164 (40), 163 (45), 161 (25), 133 (20), 105 (25), 99 (100). HREIMS 280.2053 ($C_{17}H_{28}O_3$ requires 280.2038).

Treatment of 2β-methoxyclovane-9α-ol (4) with DBr. 2β-Methoxyclovan-9α-ol (23 mg) (**8**) was dissolved in deuteriated acetone (1.6 ml) and DBr (47 %) (1.6 ml) was added. The mixture was stirred for 18 hours. The reaction was worked up following the procedure described previously, giving 12[^{2}H]α,15[^{2}H$_3$]-9α-bromo-2β-methoxyclovane (**10**) (61%), and starting material.

12 [^{2}H]α,15 [^{2}H$_3$]-9α-Bromo-2β-methoxyclovane (7). [α]$^{25}_D$ - 11.8 (c= 6.0 mg/ml, $CHCl_3$). IR (film) 3454, 2937, 2865, 1462, 1385, 1279, 1194, 1108, 1053, 991, 946, 915, 843 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) similar to undeuteriated product except that the signal at δ_H 1.77 ppm and the signal at δ_H 1.06 ppm totally disappeared. The signal at δ_H 1.00 ppm, which corresponds to H-12β, appeared as a broad singlet. ^{13}C-

NMR ($CDCl_3$, 50 MHz) δ^{13}_C 20.4 (t, C-6), 25.3 (q, C-13), 27.0 (t, C-11), 28.7 (t, C-10), 31.1 (q, C-14), 33.5 (t, C-7), 36.7 (t, C-12), 37.0 (s, C-4), 44.1 (s, C-1), 44.3 (t, C-3), 52.0 (d, C-5), 58.3 (q, O-$\underline{C}H_3$), 68.0 (d, C-9), 89.8 (d, C-2). EIMS *m/z* (70 eV) 320 (1) $[M]^+$, 319 (1), 318 (1), 317 (0.5), 316 (0.2), 315 (0.1), 288 (0.8), 287 (0.8), 286 (1), 273 (1), 272 (1), 271 (2), 240 (2), 239 (3), 207 (6), 151 (5), 99 (100), 85 (11). HREIMS 318.1487-320.1499 ($C_{16}H_{23}OBrD_4$ requires 318.1496-320.1477). ^{2}H-NMR ($CDCl_3$, 400 MHz) δ^2_H 1.75 (s, 1^2H, ^{2}H-12α), 1.01 (s, 3 ^{2}H, ^{2}H-15).

Elimination reaction of 2β-methoxyclovane-9α-ol (4) with DEAD/triphenylphosphine [9]. 2β-Methoxyclovan-9α-ol (**4**) (129 mg) was dissolved in toluene and was stirred. To this mixture, triphenylphosphine (295 mg) and diethyl azodicarboxylate (DEAD) (0.5 ml, dropwise) were added and the resulting mixture was refluxed for 4 h. When the reaction was complete (TLC control), it was worked-up in the same way as previous procedures, to afford 2β-methoxyclovan-9-ene (**11**) (19 mg, 16%), and 1R,5S,9R-4,4-dimethyl-8-methylentricyclo [6.3.2.0 ^{1,5}] dodecane (**12**) (13 mg, 11%).

2β-Methoxyclovan-9-ene (11). $[\alpha]^{25}_D$ +0.5 (c= 9.5 mg/ml, $CHCl_3$). IR (film): 3011, 2928, 2866, 1667, 1435, 1125, 1090, 746, 698 cm^{-1}. ^{1}H-NMR ($CDCl_3$,, 400 MHz) δ_H 0.95 (s, 3H, H-15), 1.01 (s, 3H, H-14β), 1.03 (s, 3H, H-13α), 1.19 (brs, 2H, H-12), 1.27-1.22 (m, 1H, H-6β), 1.54-1.48 (m, 1H, H-6α), 1.61-1.58 (m, 1H, H-7β), 1.63 (brs, 1H, H-5), 1.72 (m, 2H, H-3, H-3'), 1.92 (dd, 1H, $J_{11\beta\text{-}12}$ = 4.7 Hz, $J_{11\beta\text{-}11\alpha}$ = 18.6 Hz, H-11β), 2.21 (td, 1H, J = 2.5 and 18.6 Hz, H-11α), 3.14 (t, 1H, J = 3.5 Hz, H-2α), 3.25 (s, 3H, OCH_3), 5.22 (md, 1H, J = 1.5 and 9.8 Hz, H-9), 5.70 (ddd, 1H, J = 2.5, 4.7 y 9.8 Hz, H-10). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ^{13}_C 20.1 (t, C-6), 28.0 (q, C-13), 29.8 (q, C-14) ,32.1 (s, C-8), 33.0 (q, C-15), 34.3 (t, C-7), 35.1(t, C-12), 40.3 (s, C-4), 41.0 (t, C-11), 43.4 (t, C-3), 46.9, 51.2 (d, C-5), 56.6 (q, O-CH_3), 91.0 (d, C-2), 126.5 (d, C-10), 134.6 (d, C-9). EIMS *m/z* (70 eV) 234 (7) $[M^+]$, 219 (1), 202 (100), 187 (73), 174 (15), 159 (73), 131 (29), 119 (37), 105 (44), 91 (37). HREIMS 234.1964 ($C_{16}H_{26}O$ requires 234.1984).

1R,5S,9R-4,4-Dimethyl-8-methylentrycyclo [6.3.2.0^{1,5}] dodecane (12). $[\alpha]^{25}_D$ - 3.4 (c= 0.9 mg/ml, $CHCl_3$). IR (film) 2928, 2866, 1656, 1562, 1389, 1462, 1113, 885 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ_H 0.78 (s, 3H, H-13α), 0.96 (s, 3H, H-14β), 1.47-1.34 (m, 2H, H-10 , H-3'), 1.83 (dd, 1H, J= 6.1, 11.9 Hz, H-3), 2.28 (dd, 1H, J= 6.0, 10.5 Hz, H-2α), 2.29 (dt, J= 2.0, 17.5 Hz, H-12'), 2.48 (m, 2H, H-9β and H-12), 3.32 (s, 3H, O$\underline{C}H_3$), 4.65 (dd, 1H, J= 2.1, 4.1 Hz, H-15'), 4.71 (dd, 1H, J= 2.3, 4.3 Hz, H-15). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ^{13}_C 21.3 (t, C-6), 23.3 (q, C-13), 28.3 (t, C-7), 29.2 (t, C-11), 29.7 (q, C-14), 29.9 (s, C-1), 37.4 (t, C-3), 40.1 (d, C-8), 41.1 (t, C-11), 45.4 (t, C-9), 56.6 (d, C-5), 58.2 (q, O$\underline{C}H_3$), 89.5 (d, C-2), 108.0 (t, C-15). EIMS *m/z* (70 eV) 234 (13) $[M^+]$, 219 (7), 202 (18), 187 (12), 151 (14), 99 (40), 83 (54), 69 (70), 55 (100). HREIMS 234.1986 ($C_{16}H_{26}O$ requires 234.1984).

Empirical formula	$C_{15}H_{26}O$	**Index ranges**	0 <= h <= 16, -16 <= k <= 14, -7 <= l <= 7
Formula weight	222.4	**Reflections collected**	3894
Temperature	293(2) K	**Independent reflections**	2493 [R(int) = 0.0337]
Wavelength	0.71073 Å	**Reflections with I>2sigma(I)**	1583
Crystal system	Trigonal	**Structure solution**	Direct methods
Space group	$P3_1$ (No. 144)	**Refinement method**	Full-matrix least-squares on all F^2
Unit cell dimensions	a = 14.256(6) Å ; α = 90° b = 14.256(6) Å ; β = 90° c = 6.026 Å ; χ = 120°	**Data / restraints / parameters**	2493 / 1 /145
Volume	1060.6(8) $Å^3$	**Goodness-of-fit on F^2**	1.009
Z	3	**Final R indices [I>2sigma(I)]**	R1 = 0.068, wR2 = 0.166
Density (calculated)	1.04 Mg/m^3	**R indices (all data)**	R1 = 0.111, wR2 = 0.197
Absorption coefficient	0.06 mm^{-1}	**Absolute structure parameter**	0(3)
F(000)	372	**Largest diff. peak and hole**	0.39 and -0.19 e. $Å^3$
Crystal size	0.30 x 0.10 x 0.10	**Abs. correction from psi scans**	not applied
Theta range for data collection	2 to 25°	**Maximum shift / e.s.d.**	0.03

Table 1 X-Ray crystal structure determination of compound **6a.** (The molecules are joined in spiral chains along the 3-fold screw axis by O-H...O hydrogen bonds. All non-H atoms were anisotropic. H's were included in riding mode with Uiso(H) equal to 1.2Ueq(C) or 1.5Ueq(C) for methyl groups, except for the hydroxyl H atom which was fixed at the position from a difference map with Uiso(H) equal to 1.5Ueq(O). Programs used: data collection - Enraf-Nonius CAD4 software[10]; structure solution - SHELXS-86[11]; structure refinement - SHELXL-93[12]; Interactive graphics and final drawings - CAMERON[13]. The complete crystallographic data will be deposited at the Cambridge Crystallographic Data Centre).

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