Novel Rearrangement of an Isocaryolane Sesquiterpenoid under Mitsunobu Conditions

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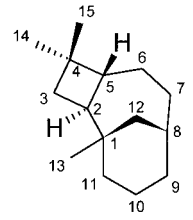
Under modified Mitsunobu reaction conditions, a novel skeleton rearrangement of terpenes has been obtained. The reactivity of 8,9-dioxygenated isocaryolane derivatives has been investigated. When either (8*R*,9*R*)-8-methoxyisocaryolane-9-ol (**7**) or (8*R*,9*R*)-isocaryolane-8,9-diol (**10**) are treated under acidic conditions, isocaryolan-9-one (**9**) and the rearrangement compound (1*S*,2*S*,5*R*,8*S*)-1,4,4-trimethyltricyclo[6.2.1.$0^{2,5}$]undecane-8-carbaldehyde (**11**) are obtained. Otherwise treatment of compounds **7** and **10** under modified Mitsunobu conditions leads to the novel sesquiterpene derivative (1*S*,2*S*,5*R*,9*R*)-1,4,4-trimethyltricyclo[7.2.1.$0^{2,5}$]dodecan-8-one (**8**). This is the first example, to our knowledge, of a Mitsunobu-induced pinacol rearrangement. The influences of the substrate and reaction conditions on the evolution of the reaction are both explored. This modification of the Mitsunobu reaction conditions introduces a new, one-pot, procedure for preparing this class of rearrangement product.

Compounds with the isocaryolane skeleton (**1**) have been obtained by rearrangement of (−)-*trans*-caryophyllene (**2**) with several electrophilic reagents,[1] through the intervention of a caryophylladiene intermediate (**3**).[2] Unlike compounds with the caryolane skeleton (**4**) which are the precursors of several tricyclic sesquiterpenoids in reactions involving electrophilic rearrangements,[3] little attention has been paid to the chemical transformation of isocaryolane derivatives.

These compounds are of interest as potential selective fungistatic agents against the plant pathogen *Botrytis cinerea*, because they possess a structural similarity to the botrylane phytotoxic metabolites produced by *B. cinerea*.[4] Some compounds which are inhibitors of the growth of *B. cinerea* have been obtained by rearrangement of isocaryophyllene (**5**) and caryophyllene oxide (**6**) in acidic media.[5]



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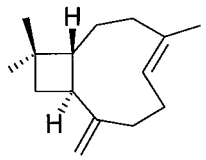

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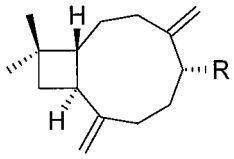
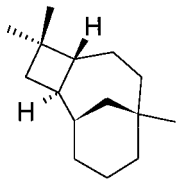


3 R = H
3a R = OH



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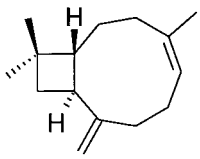

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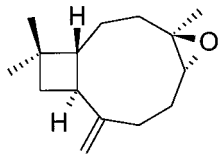

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[†] Universidad de Cadiz.
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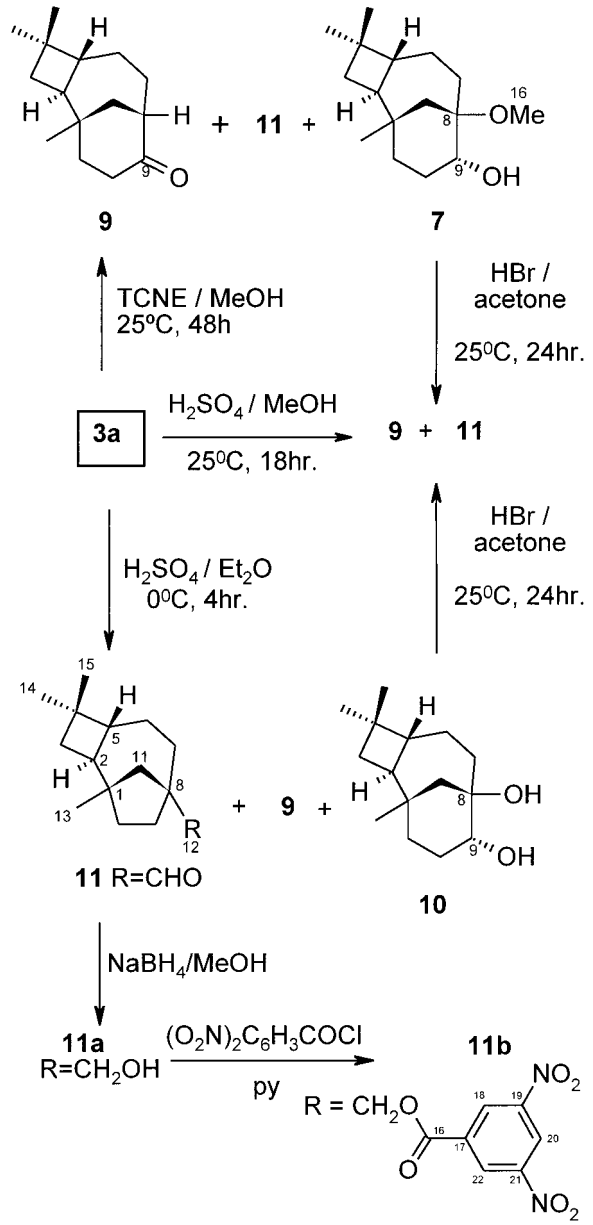
C-9, a study of the pinacol rearrangements of these isocaryolane derivatives and a novel pinacol rearrangement of (8*R*,9*R*)-8-methoxyisocaryolan-9-ol (**7**) and (8*R*,9*R*)-isocaryolane-8,9-diol (**10**) under modified Mitsunobu conditions. This rearrangement yields (1*S*,2*S*,5*R*,9*R*)-1,4,4-trimethyltricyclo[7.2.1.$0^{2,5}$]dodecan-8-one (**8**) a compound which possesses a novel sesquiterpenoid skeleton.[6]

Results and Discussion

Electrophilic reagent preferentially attack an exocyclic caryophyllene 8(12)-double bond. Only if a more reactive moiety, like a trans double bond (**1**) or a trans epoxide (**6**), is present and thermodynamic reaction conditions are used, is it possible to observe different reactivity.[2] This enabled us to direct the cyclization of appropriate derivatives of the caryophyllene skeleton to the isocaryolane skeleton, rather than to the caryolane skeleton. Treatment of compound **3a**, obtained from caryophyllene oxide (**6**),[7] with sulfuric acid in diethyl ether at 0°C for 4 h, yielded a mixture of three compounds: isocaryolan-9-one (**9**)[8] (35%), (8*R*,9*R*)-isocaryolane-8,9-diol (**10**) (45%), and an aldehydic sesquiterpenoid (**11**) (20%) (Scheme 1). When the allylic alcohol **3a** was treated with with sulfuric acid in methanol at 25 °C for 18 h, only isocaryolan-9-one (**9**) and the aldehyde **11** were obtained (Scheme 1). The structures of the products were established by spectroscopic methods. Compound **11** showed absorption at 1724 cm^{-1} in its IR spectrum, a resonance at 9.4 ppm (s, 1H) in its ^{1}H NMR, and a resonance at 204.1 ppm (d) in its ^{13}C NMR spectrum revealing the presence of an aldehyde. Nuclear Overhauser enhancement and 2D COSY studies led to an assignment of the ^{1}H NMR spectrum consistent with the structure and stereochemistry of compound **11**. Treatment of compound **11** with $NaBH_4$ in methanol gave the alcohol **11a**, which gave the crystalline derivative **11b** on treatment with 3,5-dinitrobenzoyl chloride in pyridine. The structure and stereochemistry of compound **11b** were confirmed by X-ray crystallography.[9] This in turn served to establish the structure of the parent aldehyde as (1*S*,2*S*,5*R*,8*S*)-1,4,4-trimethyltricyclo[6.2.1.$0^{2,5}$]undecane-8-carbaldehyde (**11**). A 2,4-dinitrophenylhydrazone of **11** has been described previously,[10] as a derivative of a rearrangement product of caryophyllene oxide (**6**) although there was less evidence for its structure.

The tetracyanoethylene (TCNE)-catalyzed alcoholysis of epoxides leads to ring opening[11] and selective rearrangement[7] products, but there are few reports of the use of TCNE as a catalyst for polar addition reactions to olefins.[8] We have now used TCNE to catalyze additions to double bonds. When the allylic alcohol **3a**, was treated with TCNE in methanol at room temperature (Scheme 1), the major product was a methoxy alcohol (**7**) (60%).

Scheme 1



Minor amounts of the byproducts **9** and **11** were also obtained (15% and 20%, respectively). The ^{1}H NMR of compound **7** showed resonances at 3.54 ppm (dd, 1H, *J* 5.8 and 11.2 Hz, C*H*-OH) and 3.21 ppm (s, OCH_3) assigned to H-9β and OMe, respectively. Comparison with the spectra of other compounds with the isocaryolane skeleton, together with nuclear Overhauser enhancement and 2D COSY studies, led to an assignment of the ^{1}H NMR spectrum that was consistent with the stereochemistry of compound **7** as (8*R*,9*R*)-8-methoxyisocaryolan-9-ol.

Separate treatment of (8*R*,9*R*)-8-methoxyisocaryolan-9-ol (**7**) and (8*R*,9*R*)-isocaryolane-8,9-diol (**10**) with HBr in acetone for 16 h yielded, in each case, the ketone **9** and the previously described aldehyde **11** (Scheme 1). This result is consistent with the role of 8,9-dioxygenated isocaryolanes as intermediates in the rearrangement of caryophyllane derivatives to the (1*S*,2*S*,5*R*,8*S*)-1,4,4-trimethyltricyclo[6.2.1.$0^{2,5}$]undecane-8-carbaldehyde (**11**).

Removal of methanol from (8*R*,9*R*)-8-methoxyisocaryolan-9-ol (**7**) or water from (8*R*,9*R*)-isocaryolane-8,9-diol

(6) Collado, I. G.; Hanson, J. R.; Hernandez-Galán, R.; Hitchcock, P. B.; Macías-Sánchez, A. J. and Racero, J. C. *Tetrahedron Lett.* **1999**, *40*, 6497.

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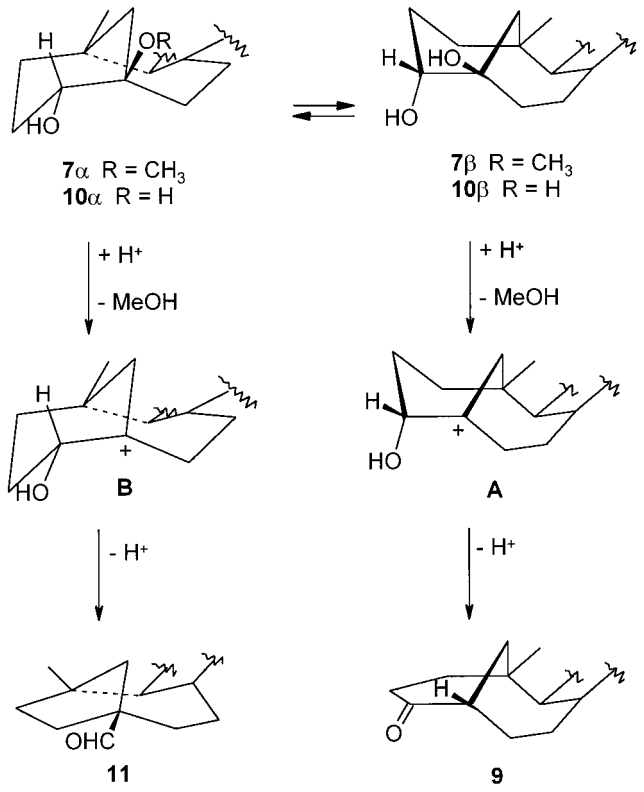
(8) Collado, I. G.; Hanson, J. R.; Hernandez-Galán, R.; Hitchcock, P. B.; Macías-Sánchez, A. J.; Racero, J. C. *Tetrahedron* **1998**, *54*, 1615.

(9) Atomic coordinates for **11b** and **13a** have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(10) Warnhoff, E. W. *Can. J. Chem.* **1964**, *42*, 1664.

(11) (a) Masaki, Y.; Miura, T.; Ochiai, M. *Synlett* **1993**, 847. (b) Masaki, Y.; Miura, T.; Ochiai, M. *Chemistry Lett.* **1993**, 17. (c) Masaki, Y.; Miura, T.; Ochiai, M. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 9. 195.

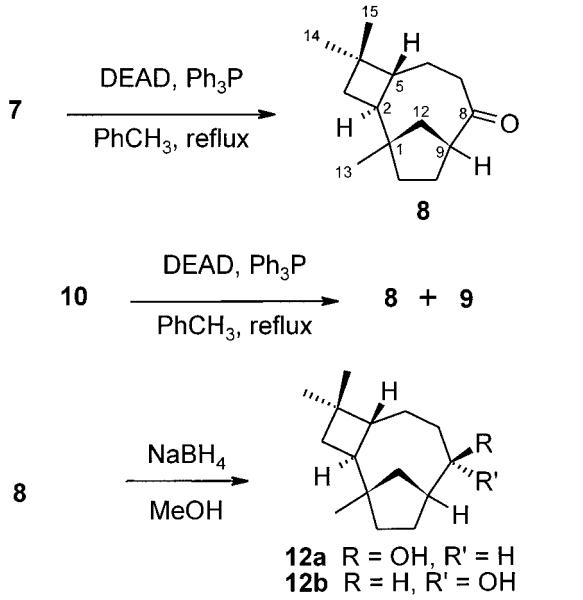
Scheme 2



(**10**) leads to two bridgehead carbocations, one from each conformation of compounds **7** or **10** (Scheme 2). The carbocation **A** may be obtained from conformation **7***β* or **10***β*. In this intermediate H-9*β* is eclipsed by the empty p-orbital at C-8 allowing a direct 1,2-hydrogen shift or a proton removal, leading in either case to the formation of isocaryolan-9-one (**9**).[12] On the other hand a bridgehead carbocation **B** may be obtained from **7**α or **10**α. This fulfils the stereoelectronic requirements for a C-10 − C-9 1,2-*σ*-bond shift leading to the aldehyde **11**.

The Mitsunobu reaction is widely used[13] in the inversion of the stereochemistry of alcohols however recently it has found application in the induction of skeletal rearrangements on terpenes.[14] Treatment of (8*R*,9*R*)-8-methoxyisocaryolan-9-ol (**7**) with diethyl azodicarboxylate (DEAD) and triphenylphosphine (Ph_3P) in toluene under reflux for 4 h yielded a product (**8**) of lower polarity on TLC (69%) (Scheme 3). On the other hand, when (8*R*,9*R*)-isocaryolane-8,9-diol (**10**) was treated under the same conditions, not only was the compound **8** obtained, but also the isocaryolane ketone **9** (Scheme 3). Compound **8** showed IR absorption at 1736 cm^{-1}, and a resonance at 219.3 ppm (s) in its ^{13}C NMR spectrum, consistent with the presence of an alicyclic ketone. Nuclear Overhauser enhancement and 2D COSY studies led to an assignment of the ^1H NMR spectrum consistent with the stereochemistry shown for compound **8**. To confirm this, compound **8** was treated with $NaBH_4$ in methanol, to give a crystalline alcohol **12a** and its epimer **12b** (Scheme 3). The structure and stereochemistry of **12a** was established

Scheme 3



by X-ray crystallography.[6] This in turn served to establish the structure and stereochemistry of **8** as (1*S*,2*S*,5*R*,9*R*)-1,4,4-trimethyltricyclo[7.2.1.$0^{2,5}$]dodecan-8-one. This compound possessed a novel sesquiterpenoid skeleton. This is the first example, to our knowledge, of a Mitsunobu-induced pinacol rearrangement.

The Mitsunobu reaction of alcohols involves the transformation of the hydroxyl group into a triphenylphosphonium derivative which acts as a leaving group and the transformation of DEAD into a reduced derivative.[15] If an N-alkylating agent is used in place of the acidic component (i.e., benzoic acid), the reaction proceeds by liberating an anion which attacks the carbon atom of the alkoxyphosphonium salt.[16] To shed some light on the mechanistic outcome of the previously described Mitsunobu reaction conditions, which did not included any acidic component, we devised some experiments involving alkylating agents.

When (8*R*,9*R*)-8-methoxyisocaryolan-9-ol (**7**) was treated with DEAD and Ph_3P in an 1:1 mixture of toluene and dichloromethane and heated to reflux for 4 h, no trace of the rearranged ketone **8** was observed, but two isomeric products (**13a** and **13b**) were obtained (Scheme 4). Only when the proportion of DEAD was increased was a small amount of the rearrangement ketone **8** obtained. The spectroscopic data of compounds **13a** and **13b** indicated an isocaryolene skeleton. They showed peaks at 272 and 270 mass units (intensity relationship 1:3), characteristic of the presence of a chlorine atom. The downfield shift of the signal corresponding to H-9 in compound **13b** (4.36 ppm) with respect to **13a** (4.19 ppm) indicated a *β*-orientation for the proton geminal to the chlorine in **13b** and then α for **13a**. Since compound **13a** was crystalline, its structure and stereochemistry were confirmed by X-ray crystallography.[9] This served to stablish the structure and stereochemistry of **13a** as (8*R*,9*S*)-9-chloro-8-methoxyisocaryolane and then as (8*R*,9*R*)-9-chloro-8-methoxyisocaryolane for compound **13b**.

Removal of a hydroxyl group from C-9 in compounds **7** or **10**, under the Mitsunobu reaction conditions, is

(12) If a proton removal is involved, ketone **9** could be formed via an enol.

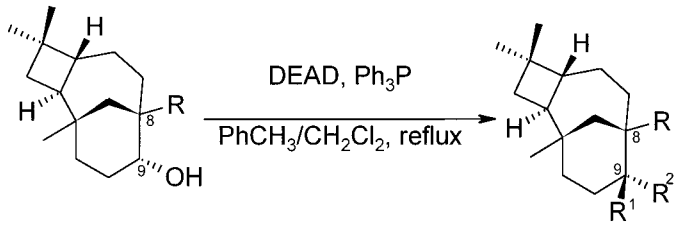
(13) Jenkins, I. D.; Mitsunobu, O. in *Encyclopaedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: New York, 1995; p 5379.

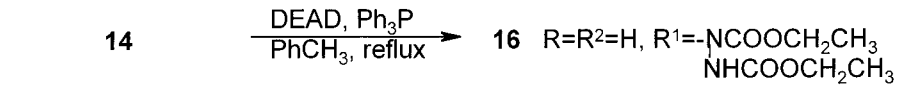
(14) Evans, P. A.; Nelson, J. D.; Rheingold, A. L. *Tetrahedron Lett.* **1997**, *38*, 2235.

(15) Mitsunobu, O. *Synthesis* **1981**, 1.

(16) Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100.

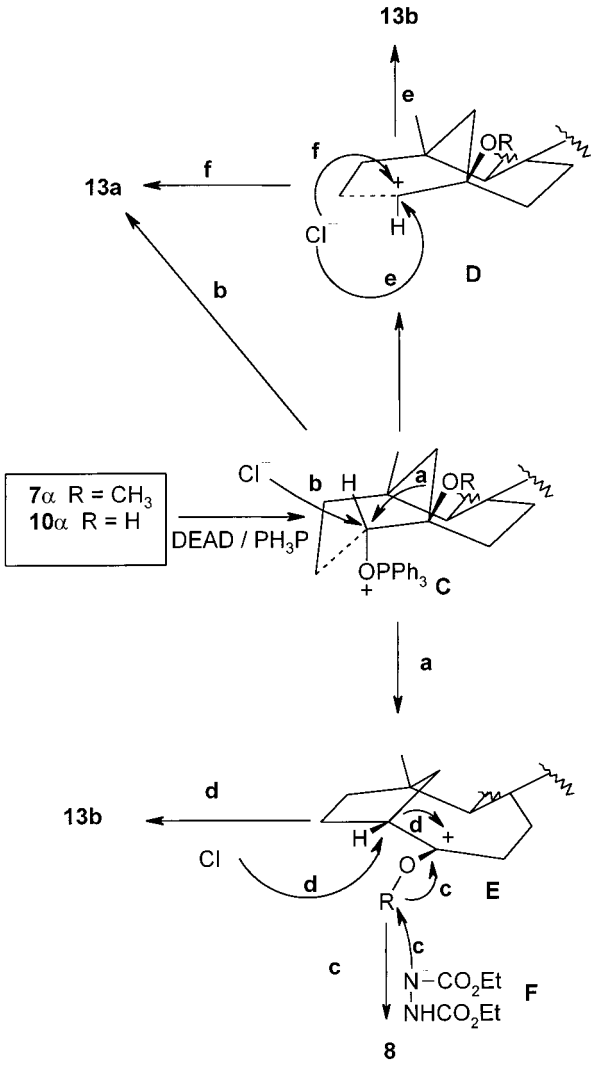
Scheme 4





mediated by a triphenylphosphonium derivative **C** (Scheme 5). This undergoes rearrangement to carbocation **E**. This rearrangement is possible because the charged derivative **C**, which comes from conformations **7**α or **10**α, possesses an anti relationship between the migrating C-12−C-8 bond and the $C_9-O(Ph_3P)^+$ bond connecting it with the leaving group. At this point, depending on the absence or not of dichloromethane as an N-alkylating agent, a different behavior is observed. If there is no source of acidity or an N-alkylating agent, the anion **F** derived from the reduction of DEAD attacks the substituent R attached to the oxygen in the stabilized carbocation **E**, leading to the ketone **8**. On the other hand, if enough dichloromethane is present, anion **F** would react with CH_2Cl_2, releasing a chloride anion. This can give the epimeric products **13a** and **13b** by two conceivable routes: (i) attack on the triphenylphosphonium ion **C** to give by direct displacement compound **13a** and attack on the intermediate **E** by a retro-pinacol rearrangement to give the product which has retained the configuration **13b**, or **(**ii) an attack on both sides of the carbocationic center of intermediate **D**, to give both **13a** and **13b**.

Scheme 5



The implication of carbocation **E** is supported by the results obtained for reactions on (9*R*)-isocaryolan-9-ol (**14**). This product, obtained by treatment of isocaryolan-9-one (**9**) with $LiAlH_4$ in diethyl ether,[8] lacks an oxygen function at C-8 preventing the occurrence of a pinacol rearrangement. Compound **14** was treated under Mitsunobu reaction conditions, with or without dichloromethane, obtaining in both cases products with inversion of the configuration at C-9 (Scheme 4). So when (9*R*)-isocaryolan-9-ol (**14**) was treated with DEAD and Ph_3P without dichloromethane, the hydrazine **16** was obtained (Scheme 4). Compound **16** showed IR absorption at 1625 cm^{-1} and ^1H NMR signals at 4.49 ppm (t, 4H, J = 7.1 Hz, −NH−CO−O−CH_2−) and 5.06 ppm (ddd, 1H, J = 5.6, 5.6 and 12.0 Hz, −C*H*−N−CO−O−; H-9α) and resonances at 159.9 ppm (s) and 160.4 ppm (s) in its ^{13}C NMR spectrum. These were consistent with presence of a bis(ethoxycarbonyl)hydrazine moiety, N-*β*-substituted at C-9 of an isocaryolane. Its structure and stereochemistry was stablished as (9*S*)-isocaryolan-9-*N*-(*N*,*N*′(diethoxycarbonyl)hydrazine) through a full set of NOE and bidimensional NMR experiments.

On the other hand when isocaryolan-9α-ol (**14**) was treated with DEAD and Ph_3P in a 1:1 mixture of toluene and dichloromethane at reflux for 4 h, the hydrazine derivative **16** was not obtained; however, a chlorinated compound (**15**) was isolated (Scheme 4). Its structure and stereochemistry was elucidated by extensive NMR and MS experiments as (9*S*)-9-chloroisocaryolane.

In conclusion, we have explored the reactivity of 8,9-dioxygenated isocaryolane derivatives, which enable the preparation of compounds with (1*S*,2*S*,5*R*,8*S*)-1,4,4-trimethyltricyclo[6.2.1.$0^{2,5}$]undecane-8-carbaldehyde (**11**) and (1*S*,2*S*,5*R*,9*R*)-1,4,4-trimethyltricyclo[7.2.1.$0^{2,5}$]dodecane (**8**) skeleta. So 8,9-dioxygenated isocaryolane compounds exhibit a different behavior depending on whether

a carbocation is generated at the C-8 or C-9 position, revealing new pathways for transformations in this class of sesquiterpene.

A pinacol rearrangement leading to compound **8**, employing a modification of the Mitsunobu conditions, introduces a new, one-pot procedure for preparing this class of rearrangement product, compared with the several-step procedures such as the Tsuchihashi method.[17]

Finally, TCNE has been employed to catalyze the electrophilic attack on double bonds, allowing the selective cyclization of compound **3a** to (8*R*,9*R*)-8-methoxyisocaryolan-9-ol (**7**).

Experimental Section

General Methods. Melting points are uncorrected. TLC was performed on Merck Kieselgel 60 F_{254}, 0.2 mm thick. Silica gel (Merck) was used for column chromatography. Purification by HPLC was accomplished using a silica gel column (Hibar 60, 7 μm, 1 cm wide, 25 cm long). Mixtures of hexane and ethyl acetate were used as solvents in the purifications.

Rearrangement of Compound 3a. Early Stage. Isocaryolan-9-one (9), (8*R*,9*R*)-Isocaryolane-8,9-diol (10), and (1*S*,2*S*,5*R*,8*S*)-1,4,4-Trimethyltricyclo[6.2.1.0^{2,5}]undecane-8-carbaldehyde (11). A solution of 96% sulfuric acid (0.5 mL) in diethyl ether (2 mL) was added to a solution of compound **3a** (500 mg) in dry diethyl ether (4 mL) at 0 °C with stirring. The mixture was kept at the same temperature, and after 4 h water was added (20 mL) with cooling. The solution was carefully brought to neutral pH with sodium carbonate. The mixture was extracted with ethyl acetate (3 × 50 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The crude reaction product was purified by column chromatography on silica gel, giving **9** (175 mg) (35%), **10** (243 mg) (45%), and **11** (100 mg) (20%). Physical data for compound **9** were identical with those described in ref 8.

(8*R*,9*R*)-Isocaryolane-8,9-diol (10): mp 115−117 °C; $[\alpha]^{25}_D$ +3 (*c* 0.5 $CHCl_3$); NMR data: Tables 1 and 3 Supporting Information; EIMS *m*/*z* (rel intensity) 238 (16) $[M^+]$, 220 (5) $[M^+ - H_2O]$, 179 (100); HREIMS 238.195 $[M^+]$ ($C_{15}H_{26}O_2$ requires 238.193).

(1*S*,2*S*,5*R*,8*S*)-1,4,4-Trimethyltricyclo[6.2.1.0^{2,5}]undecane-8-carbaldehyde (11): oil; $[\alpha]^{25}_D$ −2 (*c* 0.25 $CHCl_3$); NMR data: Tables 2 and 4 Supporting Information; EIMS *m*/*z* (rel intensity) 220(9) $[M]^+$, 191 (6) $[M - 29]^+$; HREIMS 220.179 $[M]^+$ ($C_{15}H_{24}O$ requires 220.183).

Rearrangement of Compound 3a. Late Stage. Isocaryolan-9-one (9) and (1*S*,2*S*,5*R*,8*S*)-1,4,4-Trimethyltricyclo-[6.2.1.0^{2,5}]undecane-8-carbaldehyde (11). A solution of 96% sulfuric acid (4 mL) in methanol (8 mL) was added to a solution of compound **3a** (110 mg) in methanol (5 mL) at 0 °C with stirring. The mixture was allowed to warm to room temperature, and after 16 h water was added (20 mL) with cooling. Compounds **9** (16 mg) (14%) and **11** (74 mg) (67%) were obtained when the reaction mixture was subjected to the workup described above.

(1*S*,2*S*,5*R*,8*S*)-8-Methylene-1,4,4-trimethyltricyclo-[6.2.1.0^{2,5}]undecan-15-ol (11a). Compound **11** (700 mg), dissolved in methanol (20 mL), was treated for 24 h with $NaBH_4$ (200 mg). Then, H_2O (40 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. Evaporation of the solvent afforded a crude reaction product which was purified by column chromatography on silica gel, to give compound **11a** (628 mg) (89%): mp 115−119 °C; $[\alpha]^{25}_D$ −1 (*c* 0.3 $CHCl_3$); NMR data: Tables 2 and 4 Supporting Information; EIMS *m*/*z* (rel intensity) 222 (0.7) $[M]^+$, 191 (34) $[M - 31]^+$, 106 (100); HREIMS 222.200 $[M]^+$ ($C_{15}H_{26}O$ requires 222.198).

3,5-Dinitrobenzoate of (1*S*,2*S*,5*R*,8*S*)-8-Methylene-1,4,4-trimethyltricyclo[6.2.1.0^{2,5}]undecan-15-ol (11b). Compound **11a** (25 mg), dissolved in pyridine (2 mL), was treated for 72 h with 3,5-dinitrobenzoyl chloride (50 mg). Ethyl acetate was then added, and the mixture was washed with 2 N hydrochloric acid (2 × 50 mL). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded a crude reaction product which was purified by column chromatography on silica gel, to give compound **11b** (40 mg) (85%): mp 134−137 °C; $[\alpha]^{25}_D$ −1 (*c* 0.3 $CHCl_3$); NMR data: Tables 2 and 4 Supporting Information; EIMS *m*/*z* (rel intensity) 416 (4) $[M]^+$, 191 (18), 92 (100); HREIMS 416.196 $[M]^+$ ($C_{22}O_6H_{28}N_2$ requires 416.195).

(8*R*,9*R*)-8-Methoxyisocaryolan-9-ol (7), Isocaryolan-9-one (9), and (1*S*,2*S*,5*R*,8*S*)-1,4,4-Trimethyltricyclo[6.2.1.0^{2,5}]-undecane-8-carbaldehyde (11). Compound **3a** (200 mg), dissolved in methanol (4 mL), was treated with TCNE (27 mg). After 48 h, the solvent was evaporated under reduced pressure. The resulting gum was redissolved in ethyl acetate and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded a mixture which was purified by column chromatography on silica gel, to give **7** (137 mg) (60%), **9** (30 mg) (15%), and **11** (40 mg) (20%).

(8*R*,9*R*)-8-Methoxyisocaryolan-9-ol (7): oil; $[\alpha]^{25}_D$ −12 (*c* 0.3 $CHCl_3$); NMR data: Tables 1 and 3 Supporting Information; EIMS *m*/*z* (rel intensity) 221 (9) $[M^+ + H - MeOH]$, 203 (100) $[M^+ + H - MeOH - H_2O]$; FAB-MS *m*/*z* 275 $[M + Na]^+$; HR−FAB-MS 275.198 $[M + Na]^+$ ($C_{16}NaO_2H_{28}$ requires 275.199).

Rearrangement of (8*R*,9*R*)-Isocaryolane-8,9-diol (10) and (8*R*,9*R*)-8-Methoxyisocaryolan-9-ol (7). Isocaryolan-9-one (9) and (1*S*,2*S*,5*R*,8*S*)-1,4,4-Trimethyltricyclo-[6.2.1.0^{2,5}]undecane-8-carbaldehyde (11). Compounds **7** and **10** were dissolved in acetone (20 mL) and treated with stirring with a solution of 47% HBr (30 mL) in acetone (10 mL). After 24 h, water was added (20 mL), and the solution was carefully brought to neutral pH with sodium carbonate. The mixture was extracted with ethyl acetate (3 × 50 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The crude reaction product was purified by column chromatography on silica gel, to give compounds **9** and **11**. Compound **7** (100 mg) yielded 44 mg of **9** (51%) and 19 mg of **11** (22%). Compound **10** (100 mg) yielded 46 mg of **9** (50%), and 28 mg of **11** (30%).

(1*S*,2*S*,5*R*,9*R*)-1,4,4-Trimethyltricyclo[7.2.1.0^{2,5}]dodecan-8-one (8). DEAD (0.3 mL) was added dropwise to a solution of compound **7** (200 mg) and Ph_3P (420 mg) in refluxing toluene (20 mL). The solution turned deep red as DEAD was added. After 5 h, the reaction mixture was cooled to 25 °C. Methanol (30 mL) was added, and the solvent mixture was evaporated under reduced pressure. The mixture that purified by column chromatography on silica gel, to give the starting material (50 mg) and compound **8** (91 mg) (69%): mp 132−135 °C; $[\alpha]^{25}_D$ + 2 (*c* 0.2 $CHCl_3$); NMR data: Tables 2 and 4 Supporting Information; EIMS *m*/*z* (rel intensity) 220 (17) $[M^+]$, 57 (100); HREIMS 220.184 $[M]^+$ ($C_{15}H_{24}O$ requires 220.183).

(1*S*,2*S*,5*R*,9*R*)-1,4,4-Trimethyltricyclo[7.2.1.0^{2,5}]dodecan-8-one (8) and Isocaryolan-9-one (9). DEAD (0.3 mL) was added dropwise to a solution of compound **10** (100 mg) and Ph_3P (200 mg) in refluxing toluene (20 mL). The solution turned deep red as the DEAD was added. After 5 h, the reaction mixture was cooled to 25 °C. Methanol was added (30 mL), and the solvent mixture was evaporated under reduced pressure. The mixture was purified by column chromatography on silica gel to give **8** (51 mg) (55%) and **9** (37 mg) (40%).

(1*S*,2*S*,5*R*,8*R*,9*R*)-1,4,4-Trimethyltricyclo[7.2.1.0^{2,5}]dodecan-8-ol (12a) and (1*S*,2*S*,5*R*,8*S*,9*R*)-1,4,4-Trimethyltricyclo[7.2.1.0^{2,5}]dodecan-8-ol (12b). Compound **8** (45 mg), dissolved in methanol (10 mL), was treated for 24 h with $NaBH_4$ (20 mg). Then, H_2O (30 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. Evaporation of the solvent afforded a crude reaction product which was purified by column chromatography on

(17) Tsuchihashi, G. I.; Tomooka, K.; Suzuki, K. *Tetrahedron Lett.* **1984**, *25*, 4253.

silica gel, to give compound **12a** (23 mg) (51%) and compound **12b** (7 mg) (15%).

Compound **12a**: mp 139−142 °C; $[\alpha]^{25}_D$ + 3 (*c* 0.15 $CHCl_3$); NMR data: Tables 2 and 4 Supporting Information; EIMS *m*/*z* (rel intensity) 205 (21) [M^+ − 15], 203 (12) [M^+ + H − 18], 51 (100); HREIMS 205.196 [M^+ − 15] ($C_{15}O\ H_{26}$ requires 205.196).

Compound **12b**: mp 140−144 °C; $[\alpha]^{25}_D$ −2 (*c* 0.14 $CHCl_3$); NMR data: Tables 2 and 4 Supporting Information; EIMS *m*/*z* (rel intensity) 205 (32) [M^+ − 15], 203 (18) [M^+ + H − 18], 51 (100); HREIMS 205.196 [M^+ − 15] ($C_{15}O\ H_{26}$ requires 205.196).

(8*R*,9*S*)-9-Chloro-8-methoxyisocaryolane (13a) and (8*R*,9*R*)-9-Chloro-8-methoxyisocaryolane (13b). DEAD (0.3 mL) was added dropwise to a solution of compound **7** (100 mg) and Ph_3P (210 mg) in a 1:1 mixture of refluxing dichloromethane and toluene (20 mL). The solution turned deep red as the DEAD was added. After 5 h, the reaction mixture was cooled to 25 °C. Methanol (30 mL) was added, and the solvent mixture was evaporated under reduced pressure. The mixture was purified by column chromatography on silica gel to give the starting material (25 mg), **13a** (23 mg) (29%), and **13b** (21 mg) (26%).

Compound **13a**: mp 120−123 °C; $[\alpha]^{25}_D$ +2 (*c* 0.2 $CHCl_3$); NMR data: Tables 1 and 3 Supporting Information; EIMS *m*/*z* (rel intensity) 272 (0.4) [M^+ + 2], 270 (1) [M^+], 235 (6) [M^+ − Cl]$^+$, 193 (100); HREIMS 270.173 [M^+] ($C_{16}H_{27}OCl$ requires 270.175).

Compound **13b:** mp 113−117 °C; $[\alpha]^{25}_D$ −2 (*c* 0.13 $CHCl_3$); NMR data: Tables 1 and 3 Supporting Information; EIMS *m*/*z* (rel intensity) 272 (0.3) [M^+ + 2], 270 (1) [M^+], 235 (6) [M^+ − Cl], 193 (100); HREIMS 270.174 [M^+] ($C_{16}H_{27}OCl$ requires 270.175).

(8*R*,9*S*)-9-Chloro-8-methoxyisocaryolane (13a), (8*R*,9*R*)-9-Chloro-8-methoxyisocaryolane (13b), and (1*S*,2*S*,5*R*,9*R*)-1,4,4-Trimethyltricyclo[7.2.1.0^{2,5}]dodecan-8-one (8). DEAD (1 mL) was added dropwise to a solution of compound **7** (100 mg) and Ph_3P (210 mg) in a 1:1 mixture of refluxing dichloromethane and toluene (20 mL). The solution turned deep red as the DEAD was added. After 5 h, the reaction mixture was cooled to 25 °C. Methanol (30 mL) was added, and the solvent mixture was evaporated under reduced pressure. The mixture was purified by column chromatography on silica gel to give the starting material (20 mg), **8** (4 mg) (6%), **13a** (19 mg) (22%), and **13b** (16 mg) (19%).

(9*S*)-9-Chloroisocaryolane (15). DEAD (0.5 mL) was added dropwise to a solution of compound **14**[8] (50 mg) and Ph_3P (150 mg) in a 1:1 mixture of refluxing dichloromethane and toluene (20 mL). The solution turned deep red as the DEAD was added. After 7 h, the reaction mixture was cooled to 25 °C. Methanol (30 mL) was added, and the solvent mixture was evaporated under reduced pressure. The mixture was purified by column chromatography on silica gel to give the starting material (25 mg) and **15** (24 mg) (89%): oil; $[\alpha]^{25}_D$ −1 (*c* 0.12 $CHCl_3$); NMR data: Tables 1 and 3 Supporting Information; EIMS *m*/*z* (rel intensity) 242 (1) [M^+ + 2], 240 (2.8) [M^+], 205 (7) [M^+ − Cl]$^+$, 193 (100); HREIMS 240.167 [M^+] ($C_{16}H_{25}Cl$ requires 240.164).

(9*S*)-Isocaryolan-9-*N*-(*N*,*N*′(diethoxycarbonyl)hydrazine) (16). DEAD (0.5 mL) was added dropwise to a solution of compound **7** (42 mg) and Ph_3P (150 mg) in a 1:1 mixture of refluxing dichloromethane and toluene (20 mL). The solution turned deep red as the DEAD was added. After 7 h, the reaction mixture was cooled to 25 °C. Methanol (30 mL) was added, and the solvent mixture was evaporated under reduced pressure. The mixture was purified by column chromatography on silica gel to give the starting material (17 mg) and **16** (33 mg) (88%): oil; $[\alpha]^{25}_D$ −1 (*c* 0.12 $CHCl_3$); NMR data: Tables 1 and 3 Supporting Information; EIMS *m*/*z* (rel intensity) 380, 302, 226, 220, 205, 204, 198, 190, 176; HREIMS 380.268 [M^+] ($C_{21}H_{36}N_2O_4$ requires 380.267).

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Supporting Information Available: Copies of ^1H NMR and ^{13}C NMR spectra and tables of ^1H NMR and ^{13}C NMR data for compounds **7**, **8**, **10**, **11**, **11a**, **11b**, **12a**, **12b**, **13a**, **13b**, **15**, and **16**. ORTEP drawings for compounds **11b** and **13a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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