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Novel Methoxyl and Hydroxyl Directed Pinacol Rearrangements of an Isocaryolane Sesquiterpenoid under Mitsunobu Conditions

Isidro G. Collado*, James R. Hanson†, Rosario Hernández-Galán, Peter B. Hitchcock †, Antonio J. Macías-Sánchez and Juan C. Racero

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Cádiz, Apartado 40, 11510, Puerto Real, Cádiz, Spain.
† The School of Chemistry, Physics and Environmental Science, University of Sussex, Brighton, Sussex, BN1 9QJ, Great Britain.

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Abstract: Treatment of 8-methoxy-isocaryolan-9α-ol (**1**) with acid on the one hand and with diethyl azodicarboxylate (DEAD)/triphenylphosphine on the other, leads to different pinacol rearrangements of the isocaryolane skeleton. 1*S*,2*S*,5*R*,9*R*-8-oxo-1,4,4-trimethyltricyclo[7.2.1.$0^{2,5}$]dodecane (**2**), which possesses a novel sesquiterpenoid skeleton, was obtained under Mitsunobu conditions.

Keywords: Mitsunobu reactions; rearrangements; *Botrytis cinerea;* antifungals

The skeletal rearrangement of naturally derived terpenes, such as (-)-*trans*-caryophyllene, has intrigued synthetic chemists for many years.[1] Compounds with the isocaryolane skeleton are obtained by rearrangement of (-)-*trans*-caryophyllene with electrophilic reagents;[2] little attention has been paid to the chemical transformation of these derivatives.

In this paper we report a novel pinacol rearrangement of the 8-methoxyisocaryolan-9α-ol (**1**) under Mitsunobu conditions, yielding 1*S*,2*S*,5*R*,9*R*-8-oxo-1,4,4-trimethyltricyclo[7.2.1.$0^{2,5}$]dodecane (**2**), which possesses a novel sesquiterpenoid skeleton.

Treatment of the allylic alcohol **3**, obtained from caryophyllene oxide,[3] with tetracyanoethylene (TCNE) in methanol yields 8-methoxyisocaryolan-9α-ol (**1**) (60%) (scheme 1), which was subjected to pinacol rearrangement conditions. Treatment of compound **1** with HBr in acetone yielded two products, the cyclic ketone isocaryolan-9-one (**4**) (51%),[4] and 1*R*,2*S*,5*R*,8*S*-8-carbaldehyde-1,4,4-trimethyltricyclo [6.2.1.$0^{2,5}$]undecane (**5**) (22%). Nuclear Overhauser enhancement and 2D COSY studies led to a full assignment of the ^{1}H-NMR spectrum consistent with the stereochemistry of compound **5**. A 2,4-dinitrophenylhydrazone of **5** has been described[5] previously as a derivative of a rearranged product of caryophyllene oxide although there was less evidence for its structure.

In the course of our synthetic studies aimed at the synthesis of rational fungicides against the plant pathogen *Botrytis cinerea*,[6] we required the inversion of the secondary alcohol at C-9 of **1**. Treatment of compound **1** with diethyl azodicarboxylate (DEAD) and triphenylphosphine in toluene at 80°C furnished the rearranged compound **2** in 69% overall yield (scheme 1). Reduction of **2** with lithium aluminium hydride gave a crystalline alcohol, **2a**,[7] the structure and stereochemistry of which were established by X-ray crystallography (figure 1). This served to establish the structure and stereochemistry of **2** as 1*S*,2*S*,5*R*,9*R*-8-oxo-1,4,4-trimethyltricyclo[7.2.1.$0^{2,5}$]dodecane (**2**). This compound possessed a novel sesquiterpenoid skeleton. This is the first example, to our knowledge, of a Mitsunobu-induced pinacol rearrangement.

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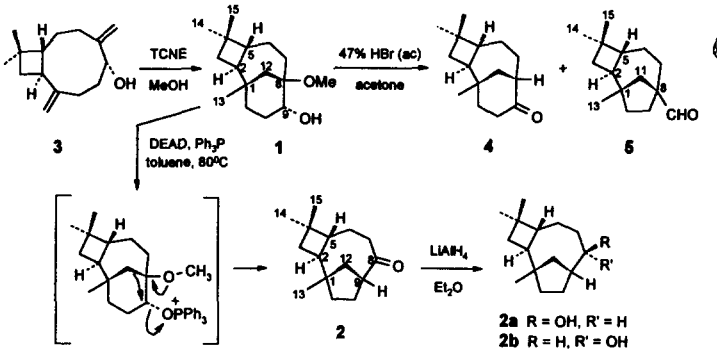
The products obtained from treatment of compound **1** with HBr can be understood in terms of the stabilities of the intermediate carbocations derived by protonation of the methoxyl group.[8] A different behaviour may be observed when a discrete carbocation is not involved. In the case of a rearrangement initiated by the hydroxyl group bonding to the triphenylphosphonium-DEAD adduct[9] the C-12 - C-8 σ-bond possesses an *anti* relationship to the leaving group. This could explain the formation of **2** that was not observed under acidic conditions. Unlike several-step procedures such as the Tsuchihashi method,[10] the DEAD/Ph_3P reaction produces an alternative route for the pinacol rearrangement in this one-pot procedure.



Scheme 1

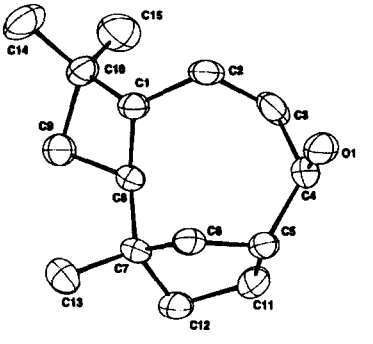


Figure 1. ORTEP drawing of **2a**

In conclusion, rearrangement of the 1,2-dioxygenated moiety on the isocaryolane skeleton (**1**) may lead either to aldehyde **5** or to the novel ketone **2**, depending on whether the reaction is initiated by attack on the methoxyl group or the hydroxyl group.

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7. ***2b:2a ratio*** = 10:3; ***overall yield*** = 65%. ***X-ray data for 2a*** : $C_{15}H_{26}O$, M = 222.4, monoclinic, space group C2 (no. 5), a = 35.52(2), b = 5.984(4), c = 14.218(4) Å, α = 90°, β = 113.07(4)°, γ = 90°, U = 2781(3) Å^3, Z = 8, T = 293(2) K, D_c = 1.06 Mg m^{-3}, μ = 0.48 mm^{-1}, 2315 reflections with 2 < θ < 60° were collected on a four-cycle diffractometer using graphite-monochromated Mo-Kα radiation. $R1$ = 0.069, $wR2$ = 0.181.
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