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Regiospecific and stereoselective ene reaction of the A-ring methylcyclohexene moiety of polycyclic terpenoid systems with dimethyl acetylenedicarboxylate

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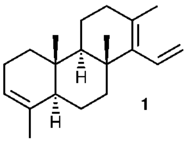
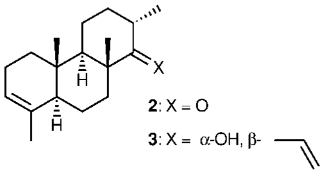
Polycyclic terpenoid compounds with a methylcyclohexene moiety at the A-ring, such as **1** and **7**, give a regio- and stereoselective ene reaction when heated at low temperatures with dimethyl acetylenedicarboxylate. The structure and stereochemistry of the compound formed in the case of **1**, e.g. **5**, is determined by X-ray analysis.

Keywords: ene reaction, dimethyl acetylenedicarboxylate, Diels-Alder reaction, phenanthrenone, scalarane

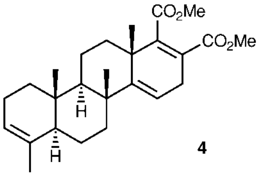
In connection with our studies on the synthesis of scalarane terpenes and related compounds[2] we investigated the Diels–Alder reaction of the 1-vinyl-2-methylcyclohexene moiety of triene **1** with dimethyl acetylenedicarboxylate (DMAD) as a simple approach to construct the D ring of the scalarane framework.[3] Contrary to our initial expectations, treatment of **1**, which is easily prepared from (S)-(+)-carvone via phenanthrenone **2**, with an excess of DMAD in a sealed tube at 110°C for 24 h, did not afford compound **4**. Instead, compound **5** was obtained, whose structure was established based on IR, MS, ^{1}H and ^{13}C NMR spectra and confirmed by X-ray diffraction (Fig. 1). The unexpected formation of this compound in the above reaction is the result of stereoselective Diels-Alder and ene reactions of the diene and A-ring methylcyclohexene moieties of **1** respectively, with DMAD. The unexpected stereochemical course of the Diels-Alder reaction, which takes place by β-approach of the dienophile *syn* to the angular methyl groups, has already been discussed for related systems.[2] Quite unexpected, given the smooth reaction conditions used, was also the facility with which the thermal ene reaction between the A-ring olefinic moiety and DMAD takes place.[4] This reaction occurs even faster than the Diels–Alder reaction, as shown by the isolation of compound **6** as the main product when compound **1** was treated with only a slight excess of DMAD at 100°C for 12 h. These smooth reaction conditions contrast with the much higher temperatures that are generally required to promote the uncatalysed ene reaction of trisubstituted alkenes.



1



2: X = O
3: X = α-OH, β-



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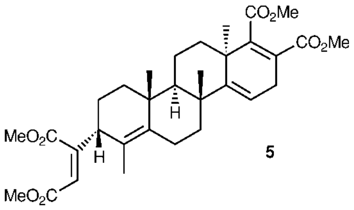

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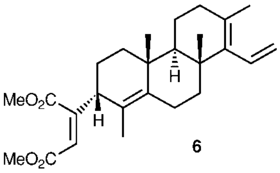

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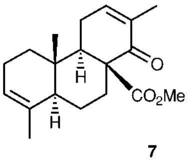

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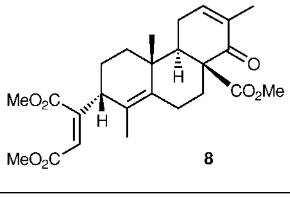

8

As in the formation of **5**, the thermal ene reaction of **1** with DMAD to give **6**, occurs via a concerted mechanism that implies the stereoselective α-approach of DMAD, *anti* to the angular methyl groups, and the regiospecific transference of the axial hydrogen from the carbon atom *trans* to the olefinic hydrogen to the enophile. The observed regiochemistry is consistent with the previous results obtained in the Lewis acid catalysed ene reaction of DMAD with related but structurally more simple methylcyclohexene systems.

As expected, the ene reaction described above for **1** also occurs easily with the A-ring double bond of other structurally related polycyclic terpenoid systems. Thus, compound 7 reacts smoothly with DMAD at 105°C to afford the ene adduct **8** in 70% yield.

The growth-inhibitory activity of some of the compounds described here was tested on some plants pathogenic fungi. Interestingly, the compounds having the dimethyl butenedioate moiety at the A-ring, *e.g.* the ene reaction products **5** and **8**, showed promising antifungal properties. In particular, compound **8** has a marked activity against *Botrytis cinerea, Monosporascus cannonballus* and *Verticillium dahliae.*

Crystallographic data and structure determination for dimethyl (Z)-2-[2,6,10,16-tetramethyl-14,15-di(methoxycarbonyl)tetracyclo[8.8.0.0^{2,7}.0^{11,16}]octadeca-6,11,14-trien-5-

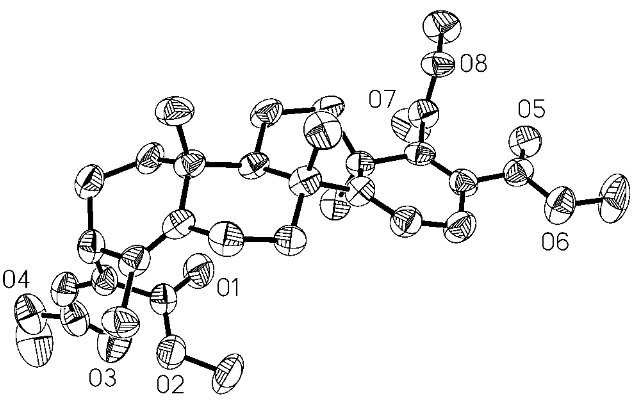

Fig. 1 Thermal ellipsoids plot of 5 (50% probability levels). Hydrogen atoms have been omitted for clarity.

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yl]-2-butenedioate (**5**): $C_{32}H_{42}O_8$, M_r = 554.66, orthorhombic, $P2_12_12_1$, *a* = 8.7987(5), *b* = 12.5480(6), *c* = 26.5634(6) Å, *V* = 2932.8(2) Å^3, *Z* = 4, D_c = 1.225, F(000) = 1192. A colourless tablet of size 0.72 × 0.70 × 0.03 mm was mounted on a glass fibre and transferred to a Nonius CAD4 diffractometer (MoKα radiation, λ = 0.71073 Å). Unit cell parameters were determined from a least-squares fit of 25 accurately centred reflections (12.3 < 2θ < 19.3). ω Scans were used to collect 9594 reflections ($2\theta_{max}$ = 50°) of which 5148 reflections were independent (R_{int} = 0.106). The structure was solved by direct methods and refined anisotropically on F2 using SHELXL-97. Hydrogen atoms were included using a riding model. The absolute structure could not be determined. The final R1 was 0.0813 for 2226 observed reflections [$I > 2\sigma(I)$] and wR_2 = 0.1604 for all reflections. A weak intermolecular Csp^3-H.···O=C hydrogen bond has been found between C(24) and O(7), thus producing zig-zag chains in the crystal packing.

Tables of atomic co-ordinates and equivalent isotropic displacement parameters (Table 1), anisotropic displacement parameters (Table 2), bond lengths and angles (Table 3), torsion angle (Table 4), and hydrogen bond (Table 5) are given at the end of the experimental section.

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Techniques used: ^{1}H and ^{13}C NMR, MS, IR, X-Ray diffraction, chromatography

References: 9

Figure 1: Thermal ellipsoids plot of **5** (50% probability levels)

Figure 2: Packing diagram of **5** showing the zigzag chains parallel to b.

Appendix: Crystal data for **5**

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