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SYNTHESIS AND MOLECULAR STRUCTURE OF METHYL (3a*S*,4*R*,7a*R*,8a*S*,8b*R*,8c*S*)-8,8-DIMETHYL-1,3,7-TRIOXO-2-PHENYL-2,3,3a,4,7,7a,8,8a,8b,8c-DECAHYDRO-1*H*-CYCLOPROPA[4,5]PYRANO[3,2-*e*]ISOINDOL-4-CARBOXYLATE

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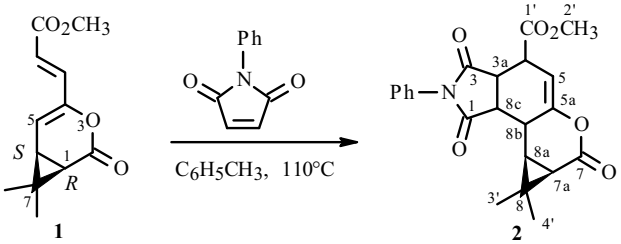
Heterocyclic compounds prepared from the monoterpene (+)-3-carene are used as intermediates in the synthesis of low-molecular-weight bioregulators and chiral ligands in asymmetric metal-complex catalysis [1]. Dienoate **1** [2] underwent a Diels–Alder reaction with *N*-phenylmaleinimide in order to synthesis new heterocyclic compounds containing a chiral monoterpene moiety. The structure of the single reaction product **2** was established using PMR and ^{13}C NMR spectroscopy and 2D methods (COSY, HSQC, NOESY) and was confirmed by an x-ray structure analysis (XSA).



The analysis of the products from [4 + 2]-cycloaddition of *N*-phenylmaleinimide to dienoate **1** must take into account that four diastereomeric adducts can form. These are products of *syn*/*anti* addition with *exo*/*endo* orientation of the phenylmaleinimide moiety relative to the cyclopropane ring. Analysis of vicinal spin–spin coupling constants (SSCCs) ($^3J_{HH}$) in PMR spectra is known to be an effective instrument for determining the stereoselectivity of cycloaddition reactions [3, 4].

The SSCCs $^3J_{8b\text{-}8c}$ = 6.0 and $^3J_{4\text{-}3a}$ = 5.8 Hz for **2** indicated that the protons were *cis*-oriented at the newly formed chiral centers C8b, C8c, C3a, and C4. This corresponded to two possible structures: *anti-exo* **2a** and *syn-endo* **2b** (Fig. 1).

The $^3J_{8b\text{-}8a}$ values could be used to assign the only obtained adduct to the *syn*- or *anti*-class. Resonances for protons H-8a and H-7a in the PMR spectrum of **2** appeared as doublets ($^3J_{8a\text{-}7a}$ = 8.0). Splitting due to spin–spin coupling with proton H-8a ($^3J_{8b\text{-}8a} \approx 0$ Hz) was not observed in the multiplet structure of the H-8b resonance. This indicated [5] that the H–C8b–C8a–H dihedral angle was close to 90°. An analysis of the dihedral angles for structures **2a** and **2b** that were obtained by optimization of the geometric parameters using the PBE/3ζ approximation [6, 7] showed that the H–C8b–C8a–H angle for **2a** was 97.5° (the product of *anti*-addition) whereas that for **2b** was –48.5°.

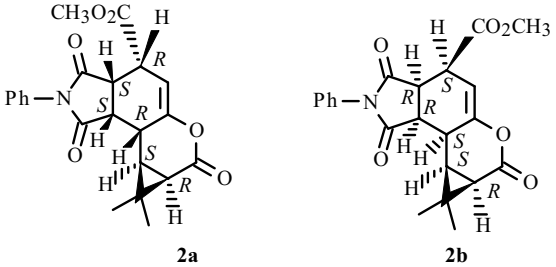


Fig. 1. Alternate structures of *anti-exo*-**2a** and *syn-endo*-**2b**.

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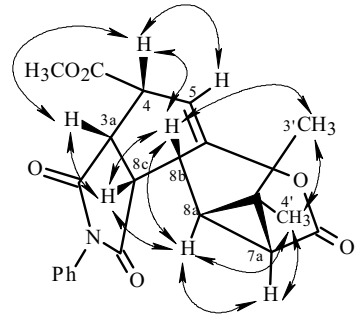

Fig. 2. Results of NOESY experiment.

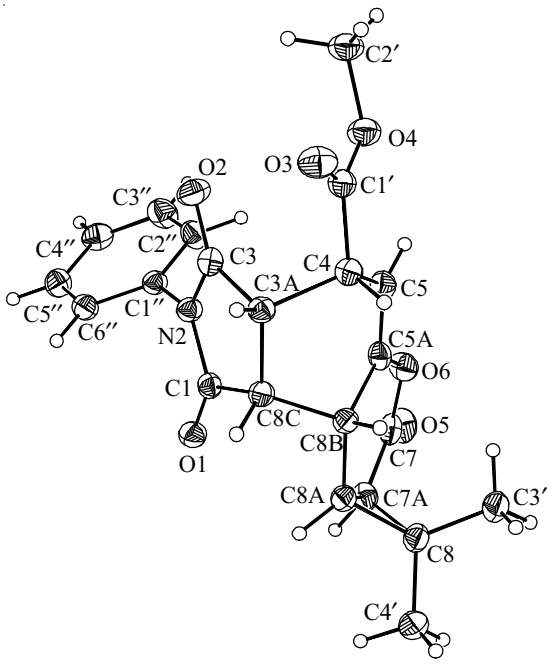

Fig. 3. General view of **2** (atoms shown as 50% probability ellipsoids).

The stereochemistry of **2** that was proposed based on the analysis of the coupling constants $^3J_{HH}$ was also confirmed by data from NOESY spectra, which appear below:

δ_H/δ_H, *ppm*	*Atom number*	δ_H/δ_H, *ppm*	*Atom number*
1.15/1.31	H-3′/H-4′	2.17/3.57	H-8a/H-8c
1.15/2.84	H-3′/H-8b	2.84/3.30	H-8b/H-4
1.31/1.87	H-4′/H-7a	2.84/3.57	H-8b/H-8c
1.31/2.17	H-4′/H-8a	3.30/3.91	H-4/H-3a
1.87/2.17	H-7a/H-8a	3.30/5.91	H-4/H-5
2.17/2.84	H-8a/H-8b	3.57/3.91	H-8c/H-3a.

The NOESY cross-peak between H-8b and H-4 and cross-peaks H-3a/H-4, H-3a/H-8c, and H-8c/H-8b confirmed the conclusion about the *cis*-orientation of protons H-8b, H-8c, H-3a, and H-4 (Fig. 2). The orientation of methine proton H-8b was established based on the NOE coupling with methyl protons H-3′, for which there were no NOESY cross-peaks with cyclopropane protons H-7a and H-8a.

PMR and ^{13}C NMR spectroscopic data obtained for **2** that characterized it as the *anti-exo* addition product **2a** agreed with results of the XSA. Figure 3 shows a general view of **2**.

The structures of all cyclic fragments were planar with the exception of the central cyclohexene, which adopted the boat conformation. The cyclopropane and cyclohexene rings were oriented on opposite sides of the lactone ring whereas the succinimide and lactone rings were situated on the same side of the cyclohexene. This corresponded to an H–C8b–C8a–H torsion angle of 91.6°. The *cis*-orientation of the protons on C8b, C8c, and C3a gave H–C3a–C8c–H and H–C8c–C8b–H torsion angles of 0.1 and –57.2°, respectively. The substituent on C4 was located in the equatorial position with an H–C3a–C4–H angle of 55.3°. The phenyl substituent on N2 was twisted relative to the succinimide ring by 63.6(3)°. This was obviously due to steric repulsion between the O atoms and the *ortho*-H atoms of the phenyl ring. The XSA data allowed the absolute configurations of the remaining chiral centers to be defined based on the known configuration of the chiral centers in the starting compound **1** ($C1_R$ and $C6_S$).

(3a*S*,4*R*,7a*R*,8a*S*,8b*R*,8c*S*)-8,8-Dimethyl-1,3,7-trioxo-2-phenyl-2,3,3a,4,7,7a,8,8a,8b,8c-decahydro-1*H*-cyclopropa[4,5]pyrano[3,2-*e*]isoindol-4-carboxylate (2) was prepared as follows. A solution of **1** (0.4 g, 1.8 mmol) in toluene (5 mL) was treated with *N*-phenylmaleinimide (0.93 g, 5.4 mmol), refluxed for 2 h, and evaporated. The solid was chromatographed over SiO_2 (eluent petroleum ether:EtOAc, 1:1) to afford **2** (0.58 g) as a white crystalline compound. Yield 82%, mp 197–198°C (EtOAc), $[\alpha]_D^{20}$ –104.8° (*c* 0.65, $CHCl_3$).

PMR and ^{13}C NMR spectra were recorded on pulsed Bruker Avance III spectrometers at operating frequency 500.13 MHz (^{1}H) and 125.47 MHz (^{13}C) using a 5-mm probe with *Z*-gradient PABBO at constant temperature 289 K. Chemical shifts in ^{13}C NMR and PMR spectra are given in ppm relative to TMS internal standard.

2D spectra were recorded in standard modes using multi-pulse sequences of the instrument software. NOESY spectra were recorded by purging a sample with dry Ar for 10 min to remove dissolved oxygen before performing the experiment.

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 1.15 (3H, s, H-3′); 1.31 (3H, s, H-4′); 1.87 (1H d, $^{3}J_{7a\text{-}8a}$ = 8.1, H-7a); 2.17 (1H, d, $^{3}J_{8a\text{-}7a}$ = 8.1, H-8a); 2.84 (1H, ddd, $^{3}J_{8b\text{-}8c}$ = 6.0, $^{4}J_{8b\text{-}5}$ = 2.6, $^{5}J_{8b\text{-}4}$ = 2.1, H-8b); 3.30 (1H, ddd, $^{3}J_{4\text{-}3a}$ = 5.9, $^{3}J_{5\text{-}4}$ = 3.9, $^{5}J_{4\text{-}8b}$ = 2.1, H-4); 3.57 (1H, dd, $^{3}J_{8c\text{-}3a}$ = 8.8, $^{3}J_{8c\text{-}8b}$ = 6.0, H-8c); 3.85 (3H, s, H-2′); 3.91 (1H, dd, $^{3}J_{3a\text{-}8c}$ = 8.8, $^{3}J_{3a\text{-}4}$ = 5.9, H-3a); 5.91 (1H, dd, $^{3}J_{5\text{-}4}$ = 3.9, $^{3}J_{5\text{-}8b}$ = 2.6, H-5); 7.14 (2H, m, H-*ortho*); 7.37 (1H, m, H-*para*); 7.43 (2H, m, H-*meta*).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.49 (C-3′), 24.25 (C-7a), 25.77 (C-8), 26.91 (C-8a), 27.28 (C-4′), 29.04 (C-8b), 40.71 (C-4), 44.03 (C-8c), 44.03 (C-3a), 52.70 (C-2′), 102.77 (C-5), 126.33 (C_{ortho}), 129.00 (C_{para}), 129.22 (C_{meta}), 131.08 (C_{ipso}), 149.92 (C-5a), 164.90 (C-7), 169.78 (C-1′), 174.80 (C-3), 174.94 (C-1).

Optimization of geometric parameters of the studied compounds, solution of the vibrational problem, and calculation of entropy and thermodynamic corrections to the total energy of the compounds were performed using the program "Priroda 06" [8] and the PBE/3ζ approximation [6, 7].

Single crystals of 2 were obtained from an EtOAc solution by slow evaporation of solvent. The crystals were colorless, $C_{22}H_{21}NO_6$ (MW = 395.40), orthorhombic, a = 7.5405(7), b = 11.2788(10), c = 22.498(2) Å, V = 1913.4(3) Å^3, space group $P2_12_12_1$, Z = 4, d_{calc} = 1.373 mg/m^3. A dataset of 21463 reflections was obtained on a Bruker Smart CCD 1000 diffractometer at 120 K (λ Mo Kα-radiation, θ_{max} = 30°). The initial dataset of measured intensities was processed using the SAINT [9] and SADABS [10] programs. The structure was solved using direct method and refined over F^2_{hkl} using anisotropic full-matrix least-squares method for non-hydrogen atoms. H atoms were placed in geometrically calculated positions and refined using a rider model [$U_{iso}(H) = nU_{eq}(C,N)$, where n = 1.5 for methyl C atoms and 1.2 for other C atoms]. The refinement used 3140 independent reflections (R_{int} = 0.0289). The refinement converged over all independent reflections with wR_2 = 0.0913 [R_1 = 0.0447 over 2836 reflections with $I > 2\sigma(I)$]. All calculations were performed on an IBM PC using the SHELXTL program set [11]. Atomic coordinates and thermal factors were deposited in the Cambridge Crystallographic Data Centre (CCDC) No. 779546; http://www.ccdc.cam.ac.uk/products/csd/request/.

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