High Pressure Organic Chemistry. Part 17.[1] Diels–Alder Reaction of Methyl Palustrate with Maleic Anhydride and *N*-Phenylmaleimide

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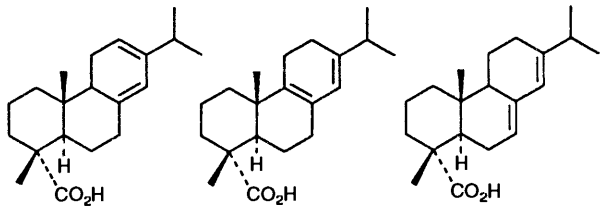
Diels–Alder reactions of methyl palustrate with a variety of dienophiles have been investigated under high pressure conditions. Thus, on reaction with maleic anhydride the adducts **5** (19%) and **6** (8%) are produced and with *N*-phenylmaleimide compound **7** (68%) is obtained. The structures and relative stereochemistry of these unprecedented adducts, **5** and **7**, are established on the basis of spectral analysis (mainly 2D NMR) and X-ray diffraction.

The ready availability from commercially available rosin of resin acids containing a reactive conjugated cyclohexadiene system has led to intensive study of their Diels–Alder reactions for the purpose of using them as starting materials for paints, varnishes and surfactants.[2] Some of these adducts can serve as synthetic intermediates for compounds containing a steroid skeleton[3] and also exhibit interesting pharmacological activity.[4] Of these dienic resin acids, however, only levopimaric acid **1** undergoes Diels–Alder reactions with dienophiles, there being no reports on the use of palustric acid **2** as a diene



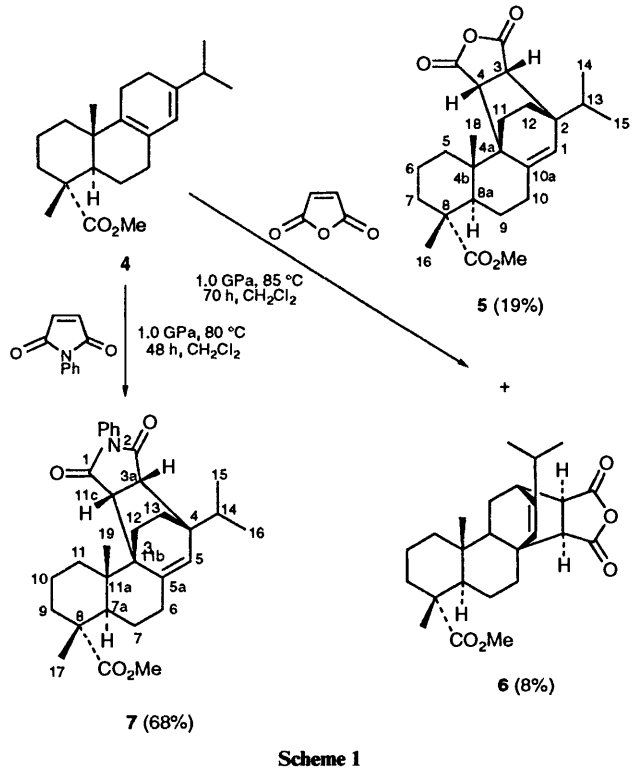
Levopimaric acid 1 Palustric acid 2 Abietic acid 3

component.[5] The main reason for this is its facile acid-catalysed isomerisation to the more stable abietic acid **3** and, possibly, due to significant steric hindrance towards dienophile attack.[2] These problems, we thought, could be overcome by the use of high-pressure techniques since the Diels–Alder reaction is favourably affected by such conditions.[6,†] In line with this reasoning, we describe here successful results for the Diels–Alder reaction of methyl palustrate **3**.‡

Results and Discussion

In order to evaluate the general reactivity of methyl palustrate **4** as a diene component, initially we attempted to induce its reaction with methyl acrylate and dimethyl maleate. In spite of numerous trials, however, no adducts were obtained. Use of dimethyl acetylenedicarboxylate was also not promising, only very small amounts of adducts being formed, the structures of which were not further investigated.§ Since Diels–Alder reactions of acetylenedicarboxylates generally proceeds with ease, this suggests the presence of a significant steric hindrance in **4**. In contrast, the reaction proceeded cleanly when **4** was treated with maleic anhydride and *N*-phenylmaleimide (Scheme 1).

Thus, the reaction of **4** with an equimolar amount of freshly sublimed maleic anhydride in dichloromethane at 1.0 GPa and 85 °C for 70 h gave a new compound **5**, m.p. 208–210 °C; $[\alpha]_D^{21}$ +57.2 (*c* 1.18, $CHCl_3$), as well as methyl maleopimarate **6**,¶ m.p. 221–222 °C (lit.,[9] 214–215 °C); $[\alpha]_D^{20}$ −28.39 (*c* 1.00, $CHCl_3$) [(lit.,[9,‖] $[\alpha]_D^{25}$ −28.7 (*c* 3.71, $CHCl_3$)], in 19 and 8% yield, respectively. The formation of **6** demonstrates that isomerisation of **3** to methyl levopimarate is favourable even under these mild conditions. The major problem encountered



Scheme 1

† The use of Lewis acid catalysts to enhance the reactivity was useless owing to its great tendency to cause isomerisation.

‡ Undoubtedly, the use of palustric acid **2** itself is unsatisfactory because of its isomerisation *via* a self-catalysation process.

§ From the ^1H NMR evidence which has a signal characteristic of an angular Me group at δ 0.64, we were able to deduce that the mixture contained the adduct derived from methyl levopimarate.[7]

¶ The complete NMR assignment of **6** using 2D NMR techniques has been reported.[8]

‖ The corresponding *exo*-isomer has m.p. 193 °C and $[\alpha]_D$ −42 (*c* 2.4, $CHCl_3$): C. Maciejewski, M. Gillard, N. Langlois and B. Gastambide, *Can. J. Chem.*, 1969, **47**, 3247.

Table 1 ^{1}H NMR data of adducts **5** and **7**[a]

	δ(ppm), multiplicity (J, Hz)		
Proton	**5**	Proton	**7**
1-H	5.78, br s	5-H	5.78, br s
3-H	3.25, A of ABq (8.4)	3a-H	3.13, A of ABq (7.2)
4-H	3.31, B of ABq (8.4)	11c-H	3.23, B of ABq (7.2)
5α-H	2.46, dd (12.4, 4.8)	11α-H	2.79, br dt (12.6, 4.8)
5β-H	1.47, dd (10.2, 4.2)	11β-H	1.5–1.6, m
6-H	1.56–1.64, m	10-H	1.6–1.7, m
7α-H	2.03, dt (12.8, 3.6)	9α-H	2.03, dt (12.4, 4.4)
7β-H	1.66, m	9β-H	1.5–1.6, m
8a-H	2.42, dd (12.6, 3.8)	7a-H	2.51, dd (12.6, 3.4)
9α-H	1.53, dt (13.6, 3.8)	7α-H	1.5–1.6, m
9β-H	1.24, m	7β-H	1.22, m
10α-H	2.38, ddt (18.0, 9.2, 2.4)	6α-H	2.39, ddt (18.0, 10.2, 2.0)
10β-H	2.58, ddt (18.0, 8.4, 2.4)	6β-H	2.65, ddt (18.0, 7.8, 2.0)
11-Ha	1.56–1.64, m	12-Ha	1.5–1.6, m
11-Hb	1.44, dt (12.4, 6.2)	12-Hb	1.45, dt (11.6, 6.4)
12-Hc	1.31, dt (12.4, 3.8)	13-Hc	1.36, dt (11.6, 2.8)
12-Hd	1.25, m	13-Hd	1.24, m
Pr^i	2.71, heptet (6.8)	Pr^i	2.86, heptet (6.8)
	0.97, d (7.2)		0.96, d (6.8)
	1.00, d (6.8)		1.04, d (7.2)
Me	16-Me, 1.29, s	Me	17-Me, 1.28, s
	17-Me, 1.09, s		19-Me, 1.10, s
CO_2Me	3.65, s	CO_2Me	3.40, s
		Ph	7.24 (2 H), m
			7.34 (1 H), m
			7.43 (2 H), m

[a] For the bicyclo[2.2.2]octene part-structure the following proton numbering is specified:

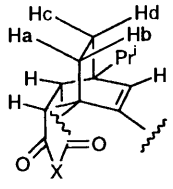


Table 2 ^{13}C NMR data of adducts **5** and **7**

Carbon	**5**[a]	Carbon	**7**[b]
1	131.21	5	131.28
2	41.89	4	42.36
3	50.24	3a	50.08
4	47.83	11c	47.43
4a	51.19	11b	51.66
4b	37.39	11a	37.46
5	32.25	11	31.87
6	18.32	10	18.14
7	35.59	9	35.44
8	47.10	8	47.15
8a	39.80	7a	39.73
9	20.55	7	21.03
10	26.92	6	27.70
10a	142.30	5a	141.69
11	27.83	12	28.43
12	21.08	13	21.03
13	29.18	14	29.53
14	16.39	15	16.51
15	18.05	16	18.31
16	18.18	17	18.32
18	21.86	19	22.19
CO_2Me	52.09, 178.85	CO_2Me	51.56, 178.99
3-CO	170.64	3	175.69
4-CO	172.50	1	177.95
		Ph	126.64, 128.21, 128.90, 132.36

[a] Recorded at 100 MHz in $CDCl_3$. [b] Recorded at 75 MHz in $CDCl_3$.

in this reaction is apparently the spontaneous isomerisation to methyl abietate, which was confirmed by capillary GLC analysis (ULBON HR-54, 50 m × 0.25 mm) from the recovered sample.[10] Therefore, it should be emphasized that use of freshly sublimed maleic anhydride is critical for formation of **5**, otherwise isomer **6** was formed exclusively. On the other hand, reaction with *N*-phenylmaleimide under similar conditions (dichloromethane, 1.0 GPa, 80 °C, 48 h) proceeded without isomerisation to furnish crystalline **7**, m.p. 158–159 °C; $[\alpha]_D^{22}$ +13.4 (*c* 0.56, $CHCl_3$), in 68% yield as the sole product.

Structures attributed to the two new adducts were originally based on NMR spectrometry using two-dimensional (2D) correlation methods.[11] Full assignments for the ^{1}H and ^{13}C NMR spectra of **5** and **7** are listed in Tables 1 and 2; the resemblance suggests that the Diels–Alder reactions resulted in identical stereochemistry. Moreover, the ^{1}H NMR signals for 3-H and 4-H of **5** or 3a-H and 11c-H of **7** exhibited a clear AB quartet pattern without additional splitting due to W-shaped coupling, hence it was concluded that they were both *endo*-adducts, following Alder's *endo*-rule.

This was supported by a 2D ^{1}H NOESY experiment; particularly noteworthy in the case of **5** were the interactions between the 5α-H and 4-H, between the 4-H and 11a-H protons, and between 3-H and 12c-H (see Fig. 1). The same situation also holds for **7**.

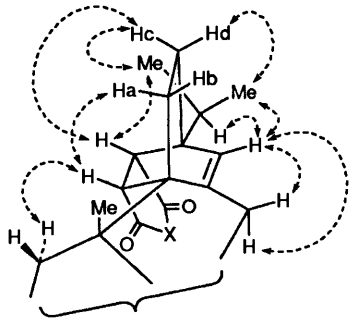


Fig. 1 Selected NOE correlations for **5** (X = O) and **7** (X = NPh)

Unambiguous confirmation for the assigned structures was obtained by a single-crystal X-ray analysis. Although the maleic anhydride adduct **5** was rather unstable and slowly decomposed at room temperature, the *N*-phenylmaleimide adduct **7** gave satisfactory orthorhombic crystals; the computer-generated ORTEP drawing is shown in Fig. 2. All bond distances and

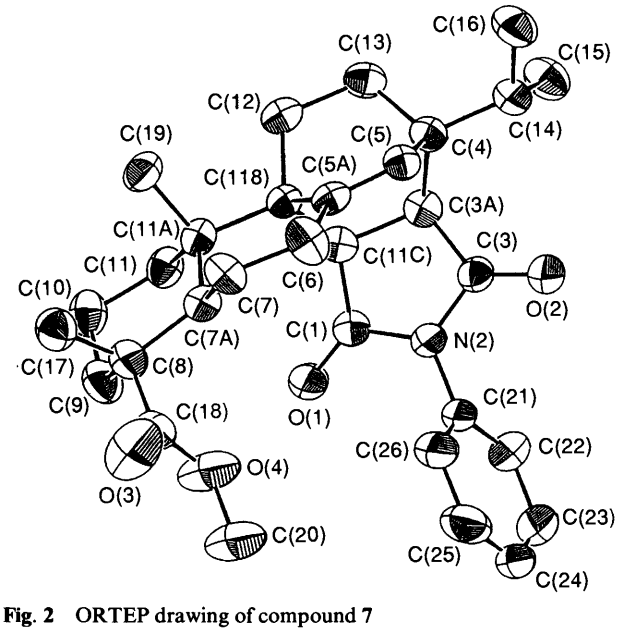


Fig. 2 ORTEP drawing of compound **7**

angles are within expected values. Interestingly, the phenyl group on nitrogen is perpendicular to the plane of the maleimide moiety, exerting a shielding effect on to the methyl ester function. While the analysis leads to the solid-state conformation of **7**, the solution conformation should not be significantly different because of the relatively rigid structure. This is supported by ^{1}H NMR results: the methyl ester of **7** shifted to higher field compared to **5** ($\Delta\delta$ 0.25 ppm).

Experimental

M.p.s are uncorrected. The NMR spectra were recorded on a Varian Unity-400 instrument (400 MHz for ^{1}H NMR analysis and 100 MHz for ^{13}C NMR analysis) or a Varian Gemini-300 spectrometer (75 MHz for ^{13}C NMR analysis). All NMR spectra were taken in $CDCl_3$ solution and are reported in ppm (δ) downfield from TMS as an internal standard. The FTIR spectra were measured with a JASCO Model FT/IR-5300 Fourier Transform Infrared Spectrometer and are reported as wavenumbers (cm^{-1}). The MS spectra were obtained on a Hewlett-Packard 5988A. Optical rotations were measured on a JASCO DIP-370 polarimeter and are recorded in units of 10^{-1} deg cm^2 g^{-1}. Thin-layer chromatography (TLC) was conducted by using Merck precoated Kieselgel 60F-254 plates (0.25 mm). PLC was carried out on 2-mm thick Merck Kieselgel 60PF-254.

All solvents were dried immediately before use. Dichloromethane was distilled from CaH_2. Methyl palustrate **3** was conventionally prepared from palustric acid **2** by the action of diazomethane in ether and was used as a high purity (>97%) sample. Maleic anhydride was used after several sublimations and *N*-phenylmaleimide was employed after recrystallisation from dry cyclohexane.

For a general procedure on high-pressure reactions, see our previous papers.[1]

Diels–Alder Reaction of Methyl Palustrate **4** *with Maleic Anhydride.*—A mixture of methyl palustrate **4** (473 mg, 1.5 mmol) and maleic anhydride (147 mg, 1.5 mmol) dry CH_2Cl_2 (0.6 cm^3) in a Teflon reaction vessel was allowed to react at 1.0 GPa and 85 °C for 70 h. After evaporation of the solvent, the crude product was purified by PLC (elution with hexane–ethyl acetate, 4:1) to give **5** (146 mg, 19%) and **6** (52 mg, 8%) along with recovered diene (279 mg, 73%; mostly methyl abietate). Analytically pure samples of **5** and **6** were obtained after recrystallisation from hexane–CH_2Cl_2.

[1R-(4aβ,4bβ,7β,10aα)]-1,2,3,4,4a,4b,5,6,7,9,10,10a-*Dodecahydro*-1-*methoxycarbonyl*-1β,4a-*dimethyl*-7-(1-*methylethyl*)-1H-4b,7-*ethanophenanthrene*-5,6-*dicarboxylic* 5,6-*Anhydride* **5**: R_f 0.37 (hexane–AcOEt, 4:1); colourless plates, m.p. 208–210 °C; $[\alpha]_D^{21}$ +57.2 (*c* 1.18, $CHCl_3$); ν_{max}(FTIR; KBr)/cm^{-1} 1827, 1771, 1730, 1717, 1460, 1225, 1074, 943 and 916; *m/z* (rel. intensity) 414 (M^+, 13), 399 (11), 354 (100), 301 (50), 256 (86), 241 (74), 185 (25), 133 (32), 91 (44) and 43 (56) [Found: C, 72.45; H, 8.3. Calc. for $C_{25}H_{34}O_5$ (414.52): C, 72.43; H, 8.27%].

^{1}H and ^{13}C NMR spectra are listed in Tables 1 and 2.

Diels–Alder Reaction of Methyl Palustrate **4** *with* N-*Phenylmaleimide.*—A mixture of methyl palustrate **4** (315 mg, 1.0 mmol) and *N*-phenylmaleimide (260 mg, 1.5 mmol) in dry CH_2Cl_2 (0.6 cm^3) in a Teflon reaction vessel was allowed to react at 1.0 GPa and 85 °C for 48 h. After evaporation of the solvent, the crude product was purified by PLC (elution with hexane–ethyl acetate, 4:1) to afford **7** (218 mg, 68%) along with the starting material (60 mg, 30%). An analytically pure sample of **7** was obtained after recrystallisation from hexane.

[3aS-(3aβ,4β,7aα,8α,11aβ,11bβ,11cβ)]-*Methyl* 1,2,3,3a,4,6,7,7a,8,9,10,11,11a,11c-*Tetradecahydro*-8,11a-*dimethyl*-1,3-*dioxo*-4-(1-*methylethyl*)-2-*phenyl*-11bH-4,11b-*ethanonaphth*[2,1-g]-*isoindole*-8-*carboxylate* **7**: R_f 0.34 (hexane–AcOEt, 4:1); colourless prisms, m.p. 158–159 °C; $[\alpha]_D^{22}$ +13.4 (*c* 0.56, $CHCl_3$); ν_{max}(FTIR; KBr)/cm^{-1} 1707, 1499, 1456, 1377 and 1182; *m/z* (rel. intensity) 489 (M^+, 15), 474 (19), 429 (46), 414 (21), 386 (5), 316 (58), 301 (50), 255 (59), 241 (90), 174 (100), 129 (51), 91 (59), 77 (56), 55 (57) and 43 (59) [Found: C, 75.90; H, 8.06; N, 3.21. Calc. for $C_{31}H_{39}NO_4$ (489.63): C, 76.04; H, 8.03; N, 2.86].

^{1}H and ^{13}C NMR spectra are listed in Tables 1 and 2.

X-Ray Determination of Compound **7**.—A colourless prismatic crystal of compound **7** having approximate dimensions of 0.40 × 0.35 × 0.30 mm, mounted on a glass fibre, was used for the X-ray study.

Crystal data. $C_{31}H_{39}NO_4$, M = 489.65, orthorhombic, space group $C222_1$, a = 16.944(3), b = 24.703(3), c = 12.481(4) Å, V = 5224(2) Å^3, Z = 8, D_c = 1.245 g cm^{-3}, F(000) 2112, μ(Cu-Kα) 6.44 cm^{-1}.

Data collection, structure solution and refinement. The intensity data were collected on a Rigaku AFC5R diffractometer with graphite monochromated Cu-Kα radiation (λ 1.541 78 Å) using ω-2θ scan technique: 1907 reflections [$I > 30\,(I)$] of 2183 unique ones, measured in the range of $2\theta \leqslant 120°$, were observed. Data were corrected for Lorentz and polarisation effects. Empirical correction for the absorption was made using the program DIFABS[12] (transmission factors: 0.80–1.26). The correction for the secondary extinction was applied (coefficient: 0.111 90E–05). The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least squares refinement was based on 1907 observed reflections [$I > 3.00\,\sigma(I)$] and 326 variable parameters and converged with unweighted and weighted agreement factors of R = 0.048 and R_w = 0.064. The standard deviation of an observation of unit weight was 1.74. The weighting scheme was based on counting statistics and included a factor (p = 0.06) to downweight the intense reflections. Plots of $\Sigma_w (|F_o| - |F_c|)^2$ *versus* $|F_o|$, reflection order in data collection, sin θ/λ, and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.21 and −0.23 e^-/Å^3, respectively. Neutral-atom-scattering factors were taken from Cromer and Waber.[13] Anomalous dispersion effects were included in F_c;[14] the values for $\Delta f'$ and $\Delta f''$ were those of Cromer.[15] All calculations were performed using the TEXSAN[16] crystallographic software package from the Molecular Structure Corporation. The ORTEP[17] program was used to obtain the drawing in Fig. 2. Tables of fractional coordinates, bond lengths and angles, thermal parameters and hydrogen atom coordinates for compound **7** have been deposited with the Cambridge Crystallographic Database.

Acknowledgements

This work was partially supported by the Ministry of Education, Science and Culture, Japan, for a Grant-in-Aid for Scientific Research [No. 05453063 (H. K.)]. We also thank Mr. M. Iwasaki for his preliminary experiments.

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Paper 3/03233G
Received 7*th June* 1993
Accepted 2*nd August* 1993