THE THREE-COMPONENT CONDENSATION OF MONOTERPENES WITH FORMALDEHYDE AND CYCLOHEXANE-1,3-DIONE. A SIMPLE ROUTE TO POLYKETIDE TERPENES

Stefan Koser and H. M. R. Hoffmann*

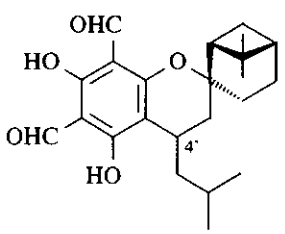
Department of Organic Chemistry, University of Hannover,
Schneiderberg 1 B, 3000 Hannover, Germany

Abstract - The framework of polyketide terpenes was obtained by the title tandem reaction which was carried out in one-pot under optimized conditions. Even tetrasubstituted olefins react, sterically hindered octahydronaphthalene (**6**) giving tetracyclic propellane (**7**).

Dedicated to Professor Alan Katritzky with best wishes on the occassion of his 65th birthday.

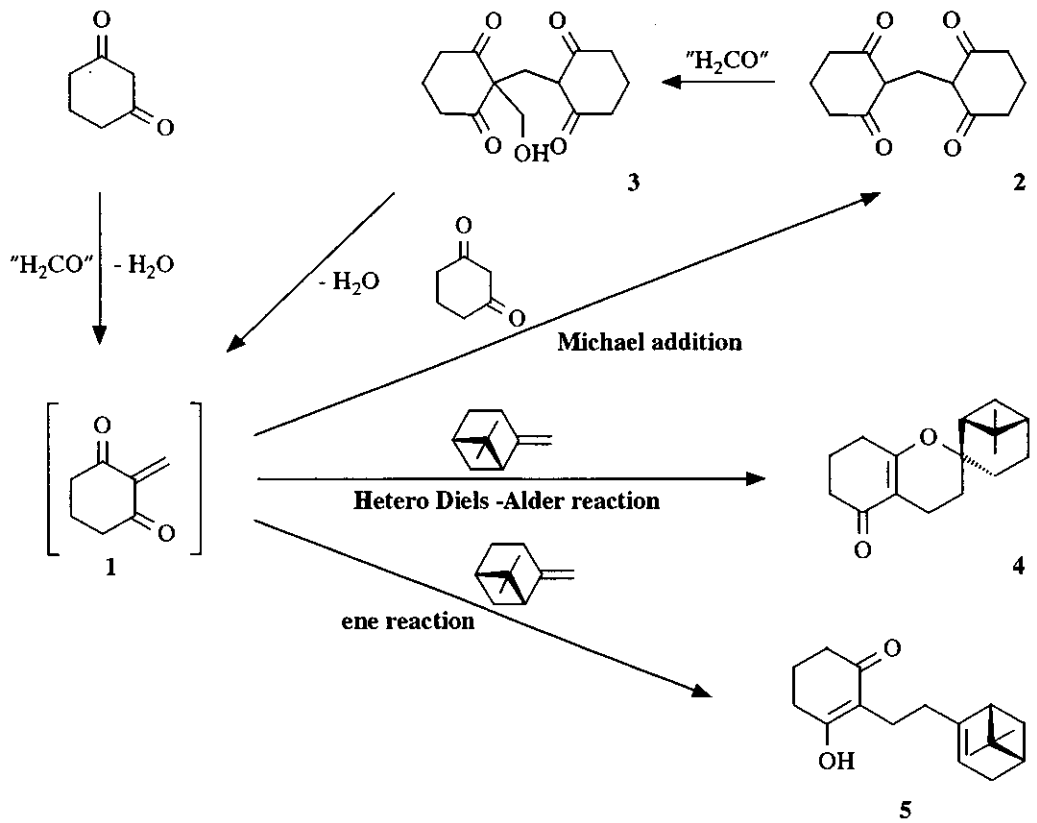
Diels-Alder reactions with simple unactivated olefins as 2π components are comparatively rare,[1,2] although intramolecular examples are known.[3a] In context with the synthesis of the robustadials[3b] (Fig. 1) we have investigated the suitability of various monoterpenes in Diels-Alder reactions with inverse electron demand. As a 4π component we chose the oxabutadiene moiety (**1**) which was generated in situ from cyclohexane-

Figure 1. Robustadial A (4'-H_α) and B (4'-H_β)



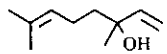
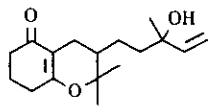
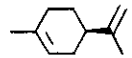
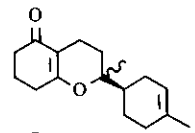
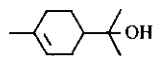
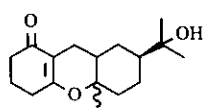
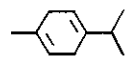
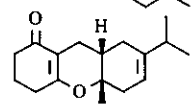
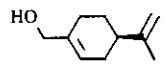
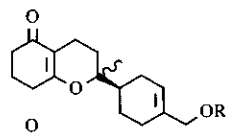
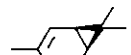
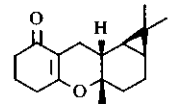
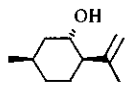
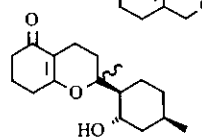
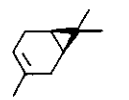
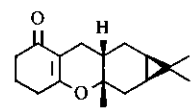
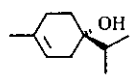
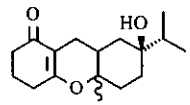
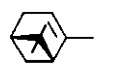
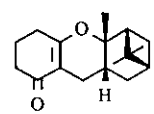
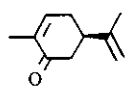
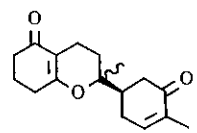
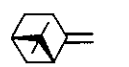
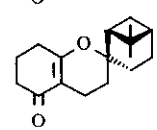
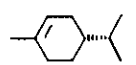
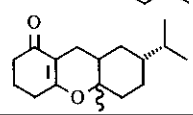
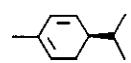
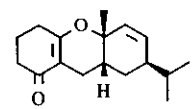
1,3-dione and paraformaldehyde under a wide variety of conditions (Scheme 1). Three reaction modes of the highly reactive oxabutadiene are possible in principle and in fact, they were all observed. The desired formation of tetracyclic adduct (**4**) was accompanied by Michael addition of cyclohexan-1,3-dione to **1**, giving adduct (**2**), which in turn reacted with another molecule of formaldehyde to afford aldol adduct (**3**).[4] Furthermore, reaction of **1** with S-(-)-β-pinene, which is well known as an efficient ene component in ene reactions,[5] afforded adduct (**5**).

Scheme 1



Under nonoptimized conditions cyclohexane-1,3-dione had disappeared within 3 min with formation of Michael adduct (**2**). Thus, the reactive intermediate (**1**) was trapped by a very fast reaction. In order to suppress the accumulation of Michael adduct (**2**) we varied the reaction conditions (solvent polarity and solvent acidity, temperature, concentration of reactants, mode of addition). In acetic acid at ~90 °C in the presence of

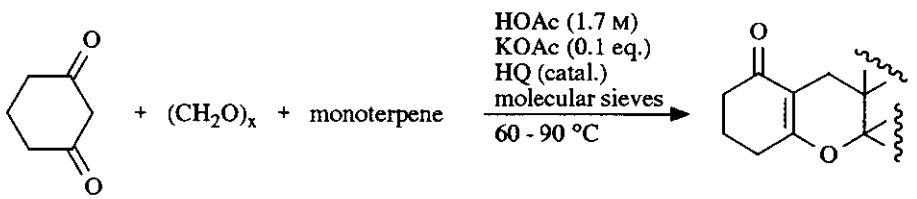
Table 1.

Terpene	t_r [h]	T [°C]	Product	Yield[a] [%]	Terpene	t_r [h]	T [°C]	Product	Yield[a] [%]
 Linalool	88	90		69 (1 : 1)	 R-(+)-Limonene	96	60		59 (1 : 1)
 α-Terpineol	96	70		69 (2.7 : 1)	 γ-Terpinene	96	70		47
 (-)-Perillyl alcohol	96	60		R = Ac 37 (1 : 1) R = H 34 (1 : 1)	 (+)-2-Carene	96	70		51
 (-)-Isopulegol	96	60		50 (1 : 1)	 (+)-3-Carene	96	80		48
 (+)-Terpen-4-ol	96	60		50 (2 : 1)	 S-(-)-α-Pinene	48	60		33
 R-(-)-Carvone	96	90		37 (1 : 1)	 S-(-)-β-Pinene	48	60		34[b]
 p-(+)-Menth-1-ene	72	90		54 (3.9 : 1)	 R-(+)-α-Phellandrene	42	60		49

[a]Diastereomeric ratio in brackets. [b]Ene product (41%) formed also; cf. Scheme 1.

potassium acetate, molecular sieves and catalytic amounts of hydroquinone the undesired adduct (**2**) was recycled *via* aldol (**3**) and retro-Michael reaction to oxabutadiene (**1**) (Scheme 2). The conditions outlined in Scheme 2 and Table 1 proved optimum.[6,7]

Scheme 2



A further side reaction was the ene reaction of **1** with monoterpene. In fact, with β-pinene formation of the ene product (41%) predominated over cycloaddition (34%).

Scheme 2 and Table 1 illustrate the wide variety of acyclic, monocyclic and bicyclic terpenes that reacted. In all cycloadditions the methylene terminus of the oxabutadiene (**1**) combined regioselectively with the less substituted terminus of a double bond.

(-)-Perillyl alcohol, R-(-)-carvone and R-(+)-limonene contain an exocyclic isoprenyl group which reacted chemoselectively at the expense of the trisubstituted, endocyclic double bond. Although the two double bonds of γ-terpinene are quite similar with respect to electron densities, the less hindered double bond reacted exclusively. On the other hand, in linalool the trisubstituted double bond was the most reactive towards **1**.

The tertiary allylic alcohol function survived the acidic conditions at 90 °C, similar to the tertiary hydroxy group in α-terpineol, (+)-terpen-4-ol, and also in (-)-isopulegol, which contains a secondary hydroxy group. The primary allylic hydroxy group in perillyl alcohol was partially acetylated.

The cycloaddition was not only regioselective and chemoselective, but also highly stereoselective. The last five monoterpenes listed in Table 1 furnished diastereomerically pure cycloadducts. These were, of course, also enantiomerically pure since the starting monoterpenes were enantiomerically pure. In each reaction, attack of the olefin proceeded cleanly from the less hindered face of the double bond. Even tetrasubstituted and sterically hindered olefins react. For example, 1,2,3,4,5,6,7,8-octahydronaphthalene (**6**) afforded oxa-propellane (**7**).[7]

In conclusion, the three component cyclocondensation of cyclohexane-1,3-dione, formaldehyde and monoterpene affords a variety of polyketide terpenes which contain naturally occurring substructures.

We thank the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft for support of our work.

REFERENCES AND NOTES

1. Reviews: D. L. Boger and S. M. Weinreb, *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press, San Diego, **1987**; cf. also L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed. Engl.*, **1993**, *32*, 131.
2. Z. M. Ismail and H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **1982**, *21*, 859; M. Krause and H. M. R. Hoffmann, *Tetrahedron Lett.*, **1990**, *31*, 6629.
3. a. L. F. Tietze, *J. Heterocycl. Chem.*, **1990**, *27*, 47.
   b. S. Koser, H. M. R. Hoffmann,and D. J. Williams, *J. Org. Chem.* **1993**, *58*, 6163.
4. Cf. J. F. Buzinkai, D. M. Hrubowchak, and F. X. Smith, *Tetrahedron Lett.*, **1985**, *26*, 3195.
5. H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **1969**, *8*, 556.
6. *General Procedure.* A two-necked flask equipped with reflux condenser was charged with cyclohexane-1,3-dione (1 eq.), paraformaldehyde (2 eq.), alkene (2 eq.), KOAc (0.1 eq.), hydroquinone (catal.), molecular sieves (2 g) and glacial acetic acid. The mixture was stirred for the indicated time, then most of the solvent was removed. The residue was diluted with CH_2Cl_2 and filtrated through celite. The filtrate was washed with sat. aq. $NaHCO_3$ (2x) and brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography. Initially, the cyclocondensation was carried out without molecular sieves, which were found to generally improve the yield. Therefore, the yields given in Table 1 are minimum yields.

   The ^{13}C nmr spectra of all cycloadducts showed the following characteristic signals: 80.8 ± 4.8 ppm (=C-O-C), 110.1 ± 1.8 ppm [-C(O)-CR=], 170.6 ± 2.2 ppm (=C-OR), 198.3 ± 0.5 ppm (C=O).

   1,2-(Dimethylmethano)-4a-methyl-2,3,4,4a,5,6,7,8,9,9a-decadehydro-1H-xanthen-8-one. Cyclohexan-1,3-dione (832 mg, 7.2 mmol), (+)-2-carene (2 g, 16.6 mmol), KOAc (71 mg) and HOAc (4.2 ml) were allowed to react according to the general procedure. Reaction time: 96 h, reaction temperature: 70 °C, white solid (955 mg, 51%). Ir (film) ν 2938, 2863, 1652, 1620, 1391, 1251, 1169, 1095; ^1H nmr (200 MHz, $CDCl_3$) δ 0.07 (dd, $^3J_{1,2}$ = 10 Hz, $^3J_{1,9a}$ = 4 Hz, 1 H, H-1), 0.41 (t, ^3J = 10 Hz, 1 H, H-2), 0.94 (s,

3 H, CH_3), 0.96 (s, 3 H, CH_3), 1.12 (s, 3 H, CH_3), 1.41 - 1.65 (m, 2 H), 1.65 - 2.07 (m, 5 H), 2.39 (m, 6 H); ^{13}C nmr (50 MHz, APT, $CDCl_3$) δ 15.25 (CH_3), 15.40 (C-3), 16.66 (C-9), 19.39 (CH_3), 21.10 (C-6), 23.97 (C-11), 24.20 (CH_3), 25.09 (C-2), 29.05 (C-5), 29.17 (C-1), 30.44 (C-9a), 34.49 (C-4), 36.81 (C-7), 76.03 (C-4a), 108.49 (C-8a), 171.37 (C-10a), 198.62 (C-8); ms (50 °C) *m/z* 261 (M^++1, 57), 246 (7), 163 (12), 136 (73), 121 (86), 93 (100). Exact mass calcd for $C_{17}H_{24}O_2$ 260.1776, found 260.1777.

6,6-Dimethyl-7',8'-[dihydrospiro[3.1.1]heptan-2,2'-chroman]-5'(6')-one. Cyclohexane-1,3-dione (497 mg, 4.3 mmol), S-(-)-β-pinene (1.8 g, 8.65 mmol), KOAc (48 mg) and HOAc (2.5 ml) were allowed to react according to the general procedure. Reaction time: 46 h, reaction temperature: 60 °C, yellow oil (375 mg, 34%). Ir ($CHCl_3$) ν 3000, 2950, 2930, 2870, 1650, 1620, 1390, 1300, 1250; ^1H nmr (200 MHz, $CDCl_3$) δ 0.98 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.52 - 1.77 (m, 3 H), 1.77 - 2.10 (m, 9 H), 2.10 - 2.42 (m, 6 H); ^{13}C nmr (50 MHz, APT, $CDCl_3$) 15.33 (C-3'), 20.99 (C-7'), 23.24 (CH_3), 24.76 (C-4), 26.38 (C-7), 27.55 (CH_3), 28.88 (C-3), 29.26 (C-8'), 32.41 (C-4'), 36.69 (C-7'), 38.16 (C-6), 40.62 (C-5), 49.53 (C-1), 84.05 (C-2'), 110.68 (C-4a'), 170.84 (C-8a'), 198.09 (C-8'); ms *m/z* 260 (M^+, 100), 217 (94), 134 (39), 92 (63), 90 (28). Exact mass calcd. for $C_{17}H_{24}O_2$ 260.1776, found 260.1777.

7. According to the general procedure[6] octahydronaphthalene (**6**) (3.8 g, 27 mmol) was allowed to react with cyclohexane-1,3-dione (1.54 g, 13.7 mmol), paraformaldehyde (0.820 g, 27.4 mmol), KOAc (0.314 g), hydroquinone (catal) and glacial acetic acid (8 ml). Reaction time: 16 h, reaction temperature: 90 °C, yield **7**: 0.42 g (12%), mp 58 °C. Ir ($CHCl_3$) ν 3002, 2942, 2868, 1614, 1392, 1185, 1134; ^1H nmr (200 MHz, $CDCl_3$) δ 0.96 - 1.86 (m, 18 H), 1.86 - 2.15 (m, 4 H), 2.24 - 2.61 (m, 4 H, H-6, H-8); ^{13}C nmr (50 MHz, APT, $CDCl_3$) δ 20.60 (C-10'), 20.84 (C-11'), 21.14 (C-7), 21.38 (C-11), 23.62 (C-10), 26.51 (C-4), 28.68 (C-8), 30.92 (C-12'), 32.01 (C-9'), 33.37 (C-3), 33.44 (C-12), 34.03 (C-9), 36.72 (C-6), 81.88 (C-2), 108.26 (C-4a), 168.91 (C-8a), 198.56 (C-5).

6 **7**

Received, 4th June, 1993