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UNACTIVATED TERPENES AS 2π COMPONENTS IN INTERMOLECULAR HETERO DIELS-ALDER REACTIONS. A SHORT STEREOCONTROLLED APPROACH TO THE ROBUSTADIAL AND EUGLOBAL SKELETON.

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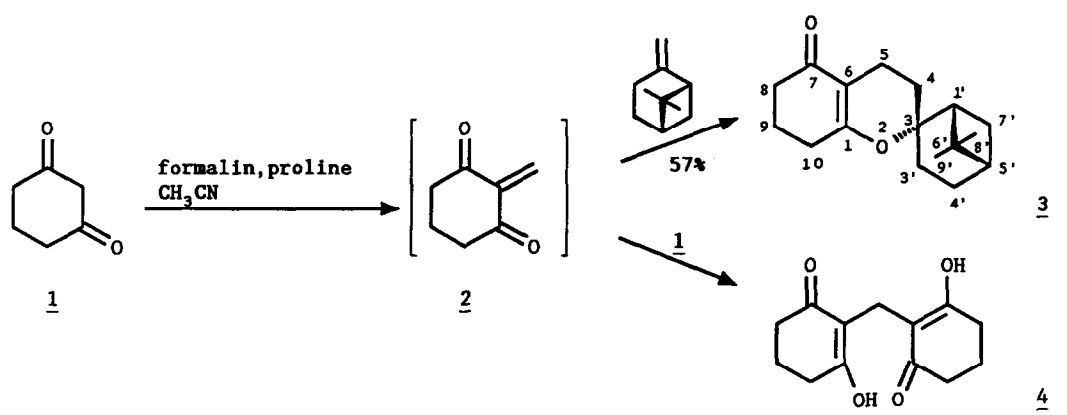
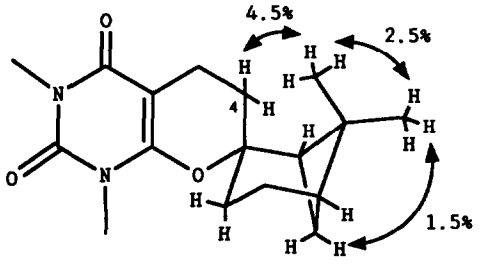
Abstract - A convergent route to the polyketide sesquiterpene skeleton of robustadial and euglobal is described.

Simple nonactivated olefins have to our knowledge not yet been used systematically in intermolecular hetero Diels-Alder (HDA) reactions with 1-oxabutadienes as 4π component, although we have shown earlier that α,β-unsaturated acyl cyanides, in the presence of $AlCl_3$, react with isobutene (2π) and also 4-methyl-1,3-pentadiene (2π) with high regioselectivity to give analogues of rose oxide.[1]

We now report examples for the intermolecular combination[2] of terpenes with activated 1-oxabutadiene equivalents. Reaction of cyclohexan-1,3-dione (**1**) with aqueous formaldehyde, proline (catal.) and β-pinene in one flask afforded tetracycle **3**. It proved advantageous to add 1,3-dione **1** to the other reactants over an extended period at 95 - 100°C. In this fashion, formation of the undesired Michael adduct **4** decreased from 37% to 12%, and tetracycle **3** was isolated in 57% yield.[3]



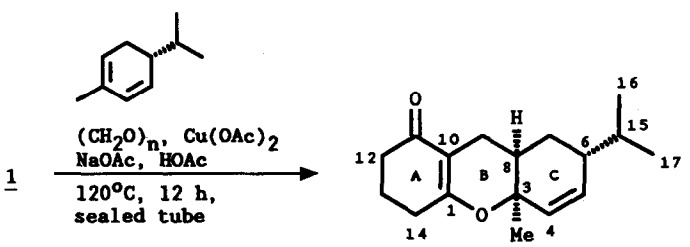
Only one spiroannulated diastereomer was formed, corresponding to diastereofacial attack of β-pinene by the 1-oxabutadiene unit from the side opposite to the hindered geminal dimethyl bridge.[5] In order to simplify the interpretation of the ^{1}H NMR spectrum, we prepared adduct 3α from dimethylbarbituric acid in analogous fashion. The nuclear Overhauser effect between methyl protons and pyran methylene protons (Fig. 1) shows the preferred stereochemical fusion of β-pinene in 3α and, by analogy, in 3.



3α

Fig. 1

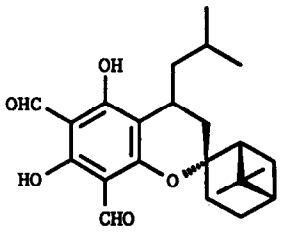
Instead of β-pinene, α-phellandrene was tried under the same conditions, but gave hardly any cycloadduct. However, using the copper acetate method, previously employed for preparing di-*t*-butyl methylenemalonate from di-*t*-butyl malonate[6] and forcing conditions (sealed tube), the desired tricycle **5** was formed stereoselectively (isopropyl group *trans* to AB moiety, cf. also **6b**) without any Michael adduct **4** in 34% yield.[7]



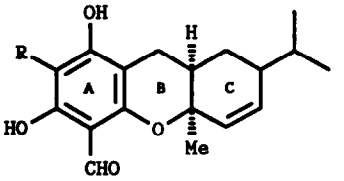
1 → 5

The new cycloadducts are useful intermediates in natural products synthesis. Tetracycle **3** contains the *trans* arrangement of spiro ether oxygen and geminal dimethyl bridge, as it occurs in robustadial (**6a**), which is used in Chinese folk medicine for the treatment of malaria.[8] By starting from optically pure (1S)-(-)-β-pinene ($[\alpha]_D^{20}$ = -21, neat) the correct absolute stereochemistry of robustadial is introduced directly (cf. Fig. 1).[9] In a total synthesis of robustadial Salomon[8b,d] has combined (+)-nopinone with a substituted 2-hydroxyacetophenone in a tandem Aldol-Michael strategy, obtaining a tetracyclic robustadial precursor as a diastereome-

ric mixture (2 : 5), the minor component leading to **6a**. The stereoselectivity of the cyclization step in the Salomon approach[8b,d] has recently been improved by Majewski and Bantle.[8e]

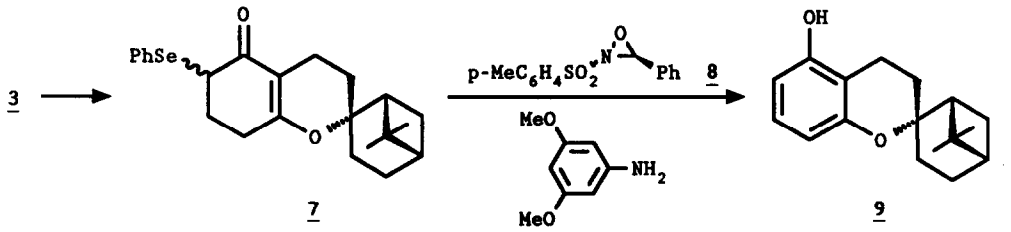


6a



6b, R = $COCH_2CH(CH_3)_2$

Because of the sensitivity of the electron rich resorcinol monoether moiety in **9** towards electrophiles and oxidizing agents, aromatization of **3** had to be carried out by oxidation of **7** with Davis reagent **8**[10,11] (*trans*-



3-phenyl-2-(*p*-toluenesulfonyl)oxaziridine) in the presence of 3,5-dimethoxyaniline.[12] Tricycle **5** has the correct ring BC substitution pattern of euglobal IIc (**6b**), which, like **6a**, is a polyketide sesquiterpene isolated from *Eucalyptus globulus*.[13]

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References and Notes

(1) Ismail, Z.M.; Hoffmann, H.M.R. *Angew.Chem., Int.Ed.Engl.* **1982**, *21*, 859. Review: Boger, D.L.; Weinreb, S.M. *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press, San Diego, 1987.

(2) Intramolecular examples: Tietze, L.F. *J.Heterocyclic Chem.* **1990**, *27*, 47.

(3) Tetracycle **3**. β-Pinene (10 mmol), **1** (10 mmol), proline (100 mg), formalin (1 mL of a 40% solution) in MeCN (5 mL) were used. Chromatography on silica gel (MTB ether/PE, 1 : 1) gave **3** (1.48 g, 57%) and **4** (0.283 g, 12%); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.39 (t, C-4), 21.05 (t, C-9), 23.25 (q, C-9′), 24.93 (t, C-4′), 26.43 (t, C-7′), 27.63 (q, C-8′), 28.80 (t, C-3′), 29.32 (t, C-10), 32.52 (t, C-5), 36.76 (t, C-8), 38.24 (s, C-6′), 40.77 (d, C-5′), 49.68 (d, C-1′), 84.07(s,

C-3), 110.77 (s, C-6), 170.71 (s, C-1), 197.91 (s, C-7) MS (70 eV, RT) *m/z* 261 (15, 260 (M^+, 100), 217 (94), 134 (39), 92 (63), 90 (28), 78 (24), 68 (24). The procedure of Stevenson for combining Meldrum's acid, CH_2O and styrene[4] gave **3** (34%) and **4** (37%).

(4) Stevenson, R.; Weber, J.V. *Heterocycl.* **1988**, *27*, 1929.

(5) Cf. the analogous behaviour of β-pinene towards enophiles in ene reactions: Hoffmann, H.M.R. *Angew.Chem., Int.Ed.Engl.* **1969**, *8*, 556.

(6) Ballesteros, P.; Roberts, B.W. *Org.Syn.* **1986**, *64*, 63.

(7) Preparation of **5**. Paraformaldehyde (300 mg, 10 mmol), **1** (560 mg, 5 mmol), (-)-α-phellandrene (680 mg, 5 mmol), $Cu(OAc)_2$ (45 mg, 0.25 mmol), NaOAc (40 mg, 0.5 mmol) and glacial AcOH (0.5 mL) were sealed at -78°C under N_2 and then heated at 120°C for 12 h. After neutralization ($NaHCO_3$) the mixture was chromatographed, giving **5**, colourless oil. 445 mg (34%); ^{13}C NMR (50 MHz, APT, $CDCl_3$) δ 19.78, 20.04 (q, C-16, C-17), 20.42 (t, C-13), 21.00 (t, C-9), 27.35 (q, C-18), 27.41 (t, C-7), 28.95 (t, C-14), 31.75 (d, C-15), 33.66 (d, C-8), 36.61 (t, C-12), 38.82 (d, C-6), 77.59 (s, C-3), 109.57 (s, C-10), 131.06, 132.64 (d, C-4, C-5), 169.56 (s, C-1), 198.22 (s, C-11); MS (70 eV, RT) *m/z* 248 (M^+, 0), 217 (3), 196 (4), 169 (3), 119 (14), 112 (21), 86 (68), 84 (100).

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(9) Optical rotation of **3**: $[\alpha]_D^{21} = -52.5$, MeOH, c = 1.18. Investigations with $Eu(hfc)_3$ on **3** did not indicate the presence of the other enantiomer. However, the diagnostically useful migrating peaks were comparatively broad multiplets.

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(11) Aromatization: Ketone **3** (1 g, 3.84 mmol) was added to LDA (1.3 eq in hexane/THF) at -78°C and stirred for 2 h. PhSeCl (770 mg, 4.04 mmol) in THF (4 mL) was added at -78°C. After 10 min the mixture was allowed to reach 0°C to 25°C. Rapid flash chromatography gave sensitive **7** (1.13 g, 2.7 mmol, 62%). Oxidation of **7** (830 mg, 2 mmol) in $CHCl_3$ (7 mL) and 3,5-dimethoxyaniline (612 mg, 4 mmol) with **8** (660 mg, 2.4 mmol) at r.t. for 1.5 h and chromatography (2x) gave **9** (235 mg, 46%); ^1H NMR (200 MHz, $CDCl_3$) δ 1.00 (s, 3 H, endo-CH_3, H-9'), 1.25 (s, 3 H, exo-CH_3, H-8'), 1.72 (d, J = 9.5 Hz, 1 H, H-7'$_{endo}$), 1.79 - 2.01 (m, 6 H, H-3, H-3', H-4'), 2.06 - 2.26 (m, 3 H, H-1', H-5', H-7'$_{exo}$), 2.63 (t, J = 7 Hz, 2 H, H-4), 5.44 (bs, 1 H, OH), 6.28 (dd, J = 8 Hz, ^4J = 1 Hz, 1 H, H-7), 6.38 (dd, J = 8 Hz, ^4J = 1 Hz, 1 H, H-9), 6.92 (t, J = 8 Hz, 1 H, H-8); ^{13}C NMR (50 MHz, APT, $CDCl_3$) δ 16.74 (t, C-3), 23.35 (q, C-9'), 24.92 (t, C-4'), 26.93 (t, C-7'), 27.71 (q, C-8'), 28.32 (t, C-3'), 32.35 (t, C-4), 38.06 (s, C-6'), 40.74 (d, C-5'), 49.31 (d, C-1'), 80.55 (s, C-2), 105.99 (d, C-7), 109.40 (s, C-5), 110.11 (d, C-9), 127.03 (d, C-8), 153.82, 155.32 (s, C-6, C-10).

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