A New Diene, 2-Methoxy-1,3-pentadiene-5-ol. Synthesis and Intramolecular Diels-Alder Reactions

Tine Jørgensen, Helle Chris Nielsen, Nageshwar Malhotra and Jan Becher*

Department of Chemistry, Odense University,
DK-5230 Odense M, Denmark

Mikael Begtrup

Department of Organic Chemistry,
Royal Danish School of Pharmacy, Universitetsparken 2,
DK-2100 Copenhagen, Denmark

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Reactions of the diene 1-benzyloxy-2-methoxy-1,3-pentadiene-5-ol in intramolecular Diels-Alder reactions using maleic anhydride or fumaric acid ethyl ester is described. The new reactive diene is prepared starting from 3-methoxypyridine. The structure of the diene was elucidated by a NOE nmr experiment.

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Introduction.

Use of the intramolecular Diels-Alder reaction (IMDA-reaction) has been found to be an effective synthetic strategy for the construction of complex natural compounds [1]. We have previously reported the synthetic applications of the *all-trans*-1-acyloxy-1,3-pentadiene-5-ol as the diene component in both inter- and intramolecular Diels-Alder- or IMDA-reactions [2]. In a recent publication by Taylor *et al.* the same skeleton has been used in the synthesis of natural compounds *pellitorin* and *sarmentine* [3], whereas Cava *et al.* uses the former diene in a Diels-Alder reaction with a thionomalemide [4].

There has been an extensive effort in preparing various dienes carrying different substituents in order to obtain functionalised cyclohexene ring systems capable to undergo further selective transformations. The well known Danischefsky's diene [5] is a good example. A trimethylsilyloxy group activates the diene system, and serves as a protected oxo function after the cycloaddition.

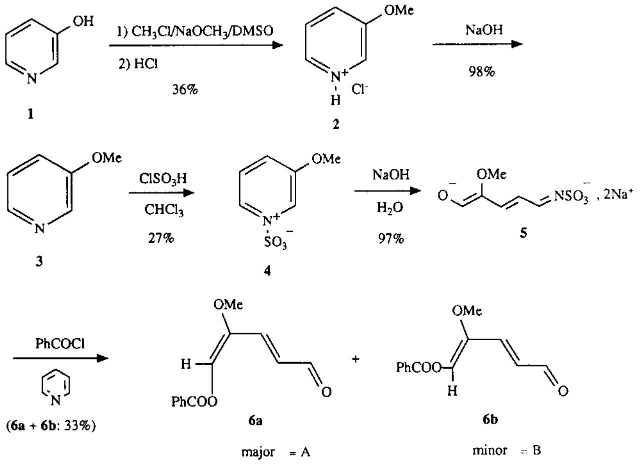
It therefore appeared of interest to investigate if an activated 1-acyloxy-2-methoxy-1,3-pentadiene-5-ol could be prepared starting from 3-methoxypyridine, and to study the applicability and reactivity of this diene in IMDA-reactions.

Results and Discussion.

Preparation of Starting Materials.

There are numerous reports [6] on the synthesis of 3-methoxypyridine. However, with the exception of the methylation of 3-hydroxypyridine [7] with diazomethane the reported yields are modest, and the methods do not appear attractive for large scale production of 3-methoxypyridine. The method we have used here is a modification of the procedure reported by Nedenskov *et al.* [8]. In a 100 g scale this method yields 36%, analytically pure 3-methoxypyridinium hydrochloride. After neutralisation of the hydrochloride, and reaction of 3-methoxypyridine with chlorosulfonic acid, 3-methoxypyridinium-1-sulfonate was obtained [9] in 27% yield. Unreacted 3-methoxypyridine can be recovered from this reaction mixture resulting in an acceptable overall yield. Ring opening of 3-methoxypyridinum-1-sulfonate with sodium hydroxide gave the disodium salt **5** in 97% yield. Benzoylation of this salt afforded 5-benzoyloxy-4-methoxy-1,3-pentadienal as a 3.8:1 mixture of the *E,Z* and *E,E* isomers (see Scheme 1). The two isomers were separated *via* preparative tlc and their structure established on the basis of the ^{1}H nmr spectra. Borohydride reduction in dry dioxane of the two isomers gave the corresponding dienols **7a** and **7b** in 90% and 100% yield, respectively. The dienols appeared to be hygroscopic and must be protected from moisture and stored in the cold under an inert atmosphere.

Scheme 1



IMDA-Reactions.

Reaction of the *E,Z*-diene alcohol **7a** and maleic anhydride in dry chloroform took place at room temperature and the resulting IMDA-product **8a** was obtained in 27% yield.

Reaction of the methoxy diene **7a** took place at room temperature, and thus confirmed that this new methoxy substituted diene system has an enhanced reactivity when compared to the similar diene devoid of the methoxy group [2]. Thus, the parent *all-trans*-1-(benzoyloxy)-1,3-pentadien-5-ol underwent IMDA-reaction with maleic anhydride only after prolonged reflux in chloroform. The modest yields of the cycloaddition products probably reflect the instability of the new diene system, as well as the fact, that the benzoyl group may not be the ideal protective group in these reactions.

When the methoxy diene **7a** was reacted with fumaric mono ethyl ester monochloride [10], the unstable triene **9a** could be isolated as an intermediate. The triene **9a** subsequently underwent intramolecular cycloaddition to the *trans*-fused lacton **10a** upon reflux in benzene. Similar reaction of the parent diene required heating to reflux in xylene [2].

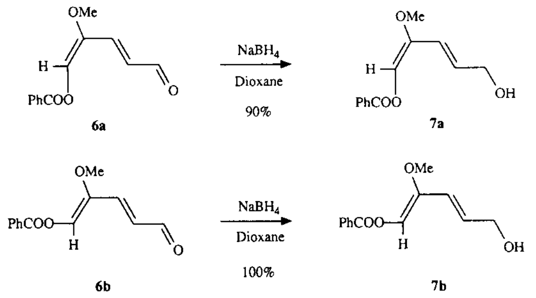
Structure of the Products.

The benzoylation reaction shown in Scheme 1, afforded two isomeric products **A** and **B**. The magnitude of the coupling between H-2 and H-3 is 15.23 Hz for **A** and 15.22 Hz for **B**. This indicates that both compounds adopts the *E*-configuration with respect to the C-2, C-3 double bond. Conventional spectroscopy did not allow determination of the configuration at the C-4, C-5 double bond. The four structures shown in Scheme 5 are all possible. This problem could however be solved by difference NOE nmr-experiments, irradiating in turn the protons of the methoxy group, all of the vinylic protons, and the aldehyde proton. As a control of the inherent background effect of the irradiation, a spectrum in which the TMS signal was irradiated was used. It was substracted computationally from the individual irradiated spectra. The resulting difference spectral express the NOE effects as positive signals. The magnitude of the NOE effect was accessed by comparison of the intensity of the signal in the difference spectrum with the intensity of the same signal in the control spectrum. The relation between the NOE effect $f_d(S)$ (%) and the distance r_{ds} (Å) between the affected and the irradiated proton is given by:

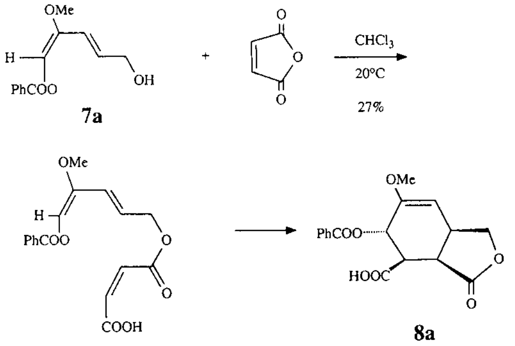
$$f_d(S)^{-1} = 2 + 1.8 \times 10^{-4} \times r^6_{ds}, \qquad [11]$$

The results for compound **A** are shown in Table 1.

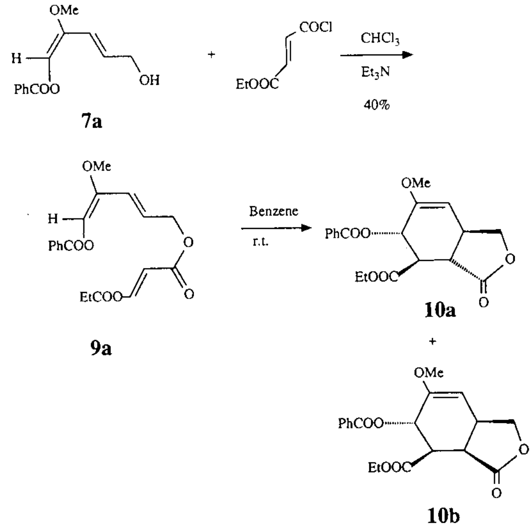
Scheme 2



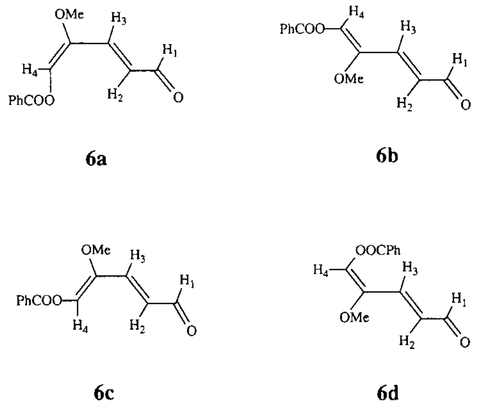
Scheme 3



Scheme 4



Scheme 5



The short distance between H-1 and H-3 (12.5% NOE by irradiation at H-1, 20.7% NOE by irradiation at H-3) indicates a *transoid* of the C-1, C-2, C-3 moiety. The much longer distance between H-2 and H-4 (0%, 0%) excludes the C-4, C-5 *Z*-configuration **6c**. Structures **6a, 6b** and **6d** are then left. The short distance between C-3 and C-4 (16.5%, 5.8%) is in favor of the all-*transoid* **6a**. Since it reacts to give a Diels-Alder product, **A** must change its conformation to **6a** prior to cyclization.

Using similar reasoning the (*Z,E*)-configuration, **6b**, can be assigned to product **B**. The NOE data for compound **B** are shown in Table 2.

Table 1a

^{1}H NMR Data and NOE Irradiation Frequencies of the Major Product **A**

Proton	δ (ppm)	J (Hz)	Irradiation frequencies (Hz)
TMS	0	[a]	4130.559
CH_3O	4.00/s	[a]	5137.639
H-2	6.51/dd	7.92/15.22	5758.671
H-3	6.90/d	15.23	5866.093
H-4	7.57/s	[a]	6012.273
arom	8.10	[a]	6166.386
H-1	9.62/d	7.97	6541.447
[a]			6630.253

[a] Negative signal. [b] No signal.

Table 1b

Observed Difference NOE Effects for the Major Product **A**

Observed Irradiated	CH_3O (%)	H-2 (%)	H-3 (%)	H-4 (%)	arom (%)	H-1 (%)
CH_3O		1.2	[b]	[a]	1.4	[b]
H-2		[a]	[a]	[b]	[b]	3.9
H-3	2.6	9.0	[a]	16.5	1.1	20.7
H-4	1.7	[b]	5.8	[a]	7.9	1.3
arom	1.1	[b]	[b]	3.6	[a]	[b]
H-1	1.1	3.5	12.5	[b]	[b]	[a]
[a]	1.1	[b]	[b]	[b]	[b]	[a]

[a] Negative signal. [b] No signal.

Table 2a

^{1}H NMR Data and NOE Irradiation Frequencies of the Minor Product **B**

Proton	δ (ppm)	J (Hz)	Irradiation frequencies (Hz)
TMS	[b]	[a]	4131.474
CH_3O	3.76/s	[a]	5075.688
H-2	6.54/dd	15.56/7.81	5762.028
H-4	7.47/s	[a]	6005.253
H-3	7.53/d	15.53	6031.193
H-1	9.74/d	7.87	6569.218
[a]			6809.086

[a] Negative signal. [b] No signal.

Table 2b

Observed Difference NOE Effects for the Minor Product **B**

Observed Irradiated	CH_3O (%)	H-2 (%)	H-4 (%)	H-3 (%)	H-1 (%)
CH_3O	[a]	[b]	24.8	[b]	[b]
H-2	3.3	[a]	[b]	7.1	6.0
H-4	1.7	19.8	[a]	[a]	6.5
H-3	2.3	[b]	[a]	[a]	11.6
H-1	1.9	[b]	[b]	9.2	[a]
[a]	1.4	[b]	[b]	[b]	[b]

[a] Negative signal. [b] No signal.

The short distance between H-1 and H-3 (9.2%, 11.6%) signals that the C-1, C-2, C-3 moiety adopts a *transoid* conformation. Short distances between respectively H-4 and H-2 (19.8%, 0%), and H-4 and the methoxy protons (24.8%, 1.7%) indicates that compound **B** adopts a C-3, C-4 *Z*-configuration in a *cisoid* conformation, and thereby must be of structure **6b**.

EXPERIMENTAL

Mass spectra were obtained on a Varian MAT 311A spectrometer. Data are reported in the form m/z. The infrared spectra (ir) were recorded on a Perkin Elmer 580 spectrophotometer. The ^{1}H nuclear magnetic resonance spectra (nmr) were recorded on either a Bruker AC 250 FT NMR spectrometer or a corresponding 300 MHz or 500 MHz apparatus. Chemical shifts are reported in parts per million (δ) with tetramethylsilane as an internal standard. The nmr signals from the phenyl groups in the products are not reported. Elemental combustion analyses were performed by NOVO A/S Copenhagen or at the University of Copenhagen. Melting points were determined on a Büchi apparatus are uncorrected.

3-Hydroxypyridine (**1**).

This compound is Aldrich, reagent grade.

3-Methoxypyridine Hydrochloride (**2**).

Sodium (48.3 g, 2.1 moles) is dissolved in methanol (520 ml) and **1** (200 g, 2.1 moles) is added to the resulting solution. After addition of dimethyl sulfoxide (DMSO) (1.0 ℓ), the methanol is removed by evaporation. At rt methylchloride (98 ml, 2.1 moles) is slowly added under vigorous stirring over 90 minutes. The temperatures is kept below 30° and the stirring is continued overnight. DMSO and 3-methoxypyridine are removed by distillation, and concentrated hydrochloric acid is added to the distillate until *p*H *ca* 4. Evaporation of the DMSO under *in vacuo* affords 110.0 g (36%) of crystalline compound **2**.

3-Methoxypyridine (**3**).

Compound **2** (110.0 g, 0.76 mole) is dissolved in 34% sodium hydroxide (70 ml) and water (120 ml). After extraction with diethylether (3 x 100 ml), the collected ether fractions are dried over potassium carbonate. Distillation yields 80.8 g (98%) of **3**, bp 64-65°.

3-Methoxypyridinium-1-sulfonate (**4**).

Compound **3** (5.5 g, 50 mmoles) is dissolved in dry chloroform (15 ml) in a round bottomed flask under magnetic stirring. *Via* a dropping funnel or a syringe chlorosulfonic acid is added during one hour at −20°. After stirring at −20° for 2-3 hours white crystals of **4** can be collected, yield 27% (2.56 g), mp 118-120°.

Disodium, 4-Methoxy-5-oxido-*trans*-2, *trans*-4-penta-1,3-dienylidenamin-*N*-sulfonate (**5**).

Under nitrogen, with magnetic stirring at −20°, sodium hydroxide (1.28 g, 32 mmoles) dissolved in water (10 ml) is added in one portion to compound **4** (2.56 g, 14 mmoles). The reaction mixture immediately turns yellow. The temperature is allowed to rise to −2° before 2-propanol (48 ml, 0°) is added. A few minutes stirring at −10° gives a yellow, crystalline, but unstable compound **5**, yield 3.32 g (97%), after filtration and drying. **Note**: The compound must be stored in a freezer under nitrogen.

5-Benzoyloxy-4-methoxypentadienal (**6a, 6b**).

Compound **5** (3.29 g, 13 mmoles) is dissolved in dry pyridine (25 ml) in a round bottomed flask, equipped with magnetic stirring, a dropping funnel and nitrogen-atmosphere. At 10-15° benzoylchloride (1.65 ml) is added dropwise in 5 minutes. After 1 hour stirring at 15° ice water is added (500 ml). When precipitation has finished, filtration affords 1.01 g (33%) crystalline mixture of the two isomers. The isomers are separated on three tlc plates, 40 cm long with a 2 mm thick layer of silica-gel using dichloromethane:ethyl acetate, 95:5 as the eluent, yielding in total 17% *E,E*-isomer **6a** and 4.6% *E,Z*-isomer **6b**.

Compound **6a** had mp 118-119°; ms: (m/z) 232 (M$^+$); ir: ν C=O 1737, 1673 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 4.00 (3H, s), 6.51 (1H, dd), 6.90 (1H, d), 7.57 (1H, s), and 9.62 (1H, d).

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.24; H, 5.17. Found: C, 67.00; H, 5.26.

Compound **6b** had mp 96-97°; ms: (m/z) 232 (M$^+$); ir: ν C=O 1733, 1673 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.76 (3H, s), 6.54 (1H, dd), 7.53 (1H, d), 7.47 (1H, s), 9.74 (1H, d).

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.24; H, 5.17. Found: C, 7.08; H, 5.24.

5-Benzoyloxy-4-methoxy-2(*E*),4(*E*)-pentadienol (**7a**).

A solution of **6a** (0.5 g, 2.2 mmoles) in dry dioxane (60 ml) is stirred in a nitrogen-atmosphere at 10° for 0.5 hour. Sodium borohydride (0.9 g, 24 mmoles) is added and the ice bath is removed after 40 minutes. The stirring is continued for three hours followed by addition of dichloromethane (50 ml) and water (50 ml). The aqueous solution is extracted with dichloromethane (2 x 60 ml) and the combined extracts are dried over sodium sulfate. Evaporation of the solvent gives **7a** as an oil, which crystallizes after prolonged drying at <0.1 mm Hg, yield 0.455 mg (90%), mp 53-54°; ms: (m/z) 234 (M$^+$); ir: ν OH 3360, C=O 1737 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.94 (3H, s), 4.26 (2H, d), 6.20 (1H, hept), 6.02 (1H, d), 7.17 (1H, s) and 2.58 (1H, br s).

Anal. Calcd. for $C_{13}H_{14}O_4+\frac{1}{2}H_2O$: C, 64.20; H, 6.17 (compound **7a** is hygroscopic). Found: C, 64.34; H, 6.16.

5-Benzoyloxy-4-methoxy-2(*E*),4(*Z*)-pentadienol (**7b**).

Similarly, a solution of **6b** (0.2 g, 0.9 mmole) yielding 0.202 g (100%) of **7b** as an oil, which can be recrystallized from cyclohexane, mp 98-100°; ms: (m/z) 234 (M$^+$); ir: ν OH 3367, C=O 1724 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.68 (3H, s), 4.32 (2H, d), 6.27 (1H, hept), 6.71 (1H, d), 7.18 (1H, s) and 2.57 (1H, br s).

Anal. Calcd. for $C_{13}H_{14}O_4+\frac{1}{3}H_2O$: C, 65.00; H, 6.11 (The compound is hygroscopic!). Found: C, 65.09; H, 6.73.

(3aα,4β,5α,7aα)-5-(Benzoyloxo)-1,3,3a,4,5,7a-hexahydro-6-methoxy-3-oxo-4-isobenzofurancarboxylic Acid (**8a**).

Under nitrogen, maleic acid anhydride (0.085 g, 0.9 mmole) is added to a solution of **7a** (0.2 g, 0.9 mmole) in dry chloroform (5 ml). After stirring for 24 hours, evaporation is followed by preparative tlc, (chloroform:methanol, 95:5) R_f = 0.09, yield 0.076 g (27%), mp 128-130°; fabms: (m/z) 333 (MH$^+$); ir: ν OH 3430, C=O 1773, 1719, 1670 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.46 (3H, s), 4.13 (1H, d), 4.45 (1H, dd), 3.40 (1H, m), 4.94 (1H, d), 5.95 (1H, d), 3.40 (1H, m), 3.61 (1H, dd) and 12.60 (1H, br s).

Anal. Calcd. for $C_{17}H_{16}O_7$: C, 61.44; H, 4.85. Found: C, 61.80; H, 4.93.

1-Benzoyloxy-2-methoxy-5-((*E*)-ethylfumaryloxy)-1(*E*),3(*E*)-pentadiene (**9**).

With stirring under nitrogen and cooling in an ice bath triethylamine (0.19 g, 1.9 mmoles) is added to a solution of **7a** (0.348 mg, 1.5 mmoles) in dry chloroform (20 ml). Fumaric acid ethyl ester monochloride (0.28 g, 1.7 mmoles) is added dropwise in 0.5 hour at 0°. Then the ice bath is removed and the reaction mixture is left for three hours. Diethyl ether is added until twice the original volume. The organic solution is washed with saturated aqueous sodium bicarbonate, distilled water and finally with saturated aqueous sodium chloride. The organic solution is dried overnight over magnesium sulfate. Evaporation and treatment with charcoal in refluxing chloroform for five minutes (**Note**: the product rearranges at higher temperatures!) followed by filtration and evaporation affords 0.212 g (40%) of the white crystalline product, mp 79-81°; ms: (m/z) 360 (M$^+$); ir: ν C=O 1714, 1725, 1733 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.96 (3H, s), 4.80 (2H, d), 6.12 (1H, t), 6.06 (1H, d), 7.21 (1H, s), 3.46-3.76 (2H, m), 4.27 (2H, q) and 1.33 (3H, t).

Anal. Calcd. for $C_{19}H_{20}O_7$: C, 63.33; H, 5.59. Found: C, 62.71; H, 5.62.

(3aβ,4β,5α,7aα)-5-(Benzoyloxy)-1,3,3a,4,5,7a-hexahydro-6-methoxy-3-oxo-4-isobenzofurancarboxylic Acid Ethyl Ester (**10a**) and (3aα,4β,5α,7aα)-5-(Benzoyloxy)-1,3,3a,4,5,7a-hexahydro-6-methoxy-3-oxo-4-isofurancarboxylic Acid Ethyl Ester (**10b**).

Under nitrogen compound **9** (0.058 mg, 0.16 mmole) is dissolved with stirring in dry benzene (10 ml). A few crystals of 2,6-di-*tert*-butyl-*p*-cresol are added as an antioxidant. The reaction mixture is refluxed at 80° for 24 hours. The two products are separated by preparative tlc eluating twice with chloroform. This gives 0.022 g (38%) of **10a** and 0.0095 g (16%) of **10a**.

The physical data, for **10a** are (chloroform:methanol, 95:5) R_f = 0.67, mp 57-58°; ms: (m/z) 360 (M$^+$); ir: ν C=O 1790, 1736 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.54 (3H, s), 4.52 (1H, m), 4.00 (1H, m), 3.27 (1H, m), 6.13 (1H, d), 5.01 (1H, d), 3.07 (1H, m), 2.96 (1H, m), 4.03 (2H, q) and 1.08 (3H, t); Cald. for $C_{19}H_{19}O_7$: 360.120905; Found: 360.1209 (peack match).

Physical data for **10b** are (chloroform:methanol, 95:5) R_f = 0.72, mp 78-79°; ms: (m/z) 360 (M$^+$); ir: ν C=O 1788, 1736 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.50 (3H, s), 4.52 (1H, m), 4.10 (1H, m), 2.93 (1H, m), 6.00 (1H, d), 5.83 (1H, d), 3.78 (1H, m), 3.30

(1H, m), 4.22 (2H, q) and 1.08 (3H, t, CH_3CH_2); Calcd. for $C_{19}H_{19}O_7$: 360.120905; Found: 360.1205 (peak match).

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