A Novel Aldol Condensation Alternative: α,β-Unsaturated Aldehydes from 3-Hydroxy-1-alkynes via Dihydrodioxepins

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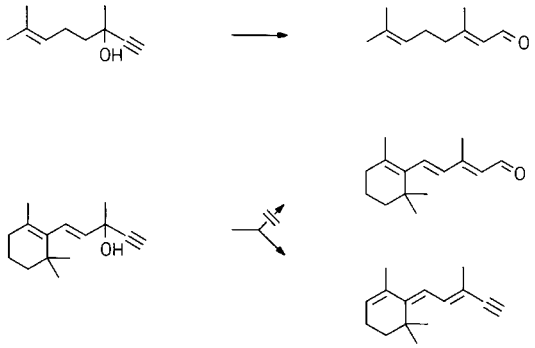
Abstract: The controlled aldol condensation between an aliphatic ketone and an acetaldehyde equivalent remains a challenge. One solution to this evergreen problem consists of the nucleophilic addition of acetylene to the ketone and the subsequent isomerization of the resulting 3-hydroxy-1-alkyne to the corresponding 2-alkenal. So far, however, the latter step could only be executed with acid-insensitive substrates. We now present a milder, three-step method which extends the scope of the procedure considerably. In the first step, the 3-hydroxy-1-alkynes are converted into 2-propynyl ethylene glycol monoethers; these then undergo base-catalyzed cyclization to give the dihydro-1,4-dioxepins, which are hydrolyzed in acidic medium in the third and final step.

Keywords: aldehydes · aldol condensation · alkynes · enethers · retinoids

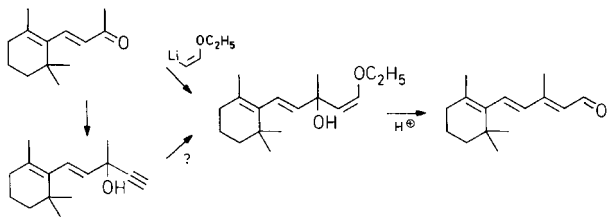
Introduction

Terminal alkynes can be hydrated under acid and mercuric salt catalysis to afford 2-alkanones.[1] In contrast, a simple method is lacking that would allow the generation of aldehydes from 1-alkynes. Such a transformation, however, can be accomplished with 3-hydroxy-1-alkynes as the substrates, as has been demonstrated by Pauling et al.[2] In the presence of a silylated vanadium catalyst, the alkynol isomerizes, presumably through an allenol intermediate, to the α,β-unsaturated aldehyde. For example, 3,7-dimethyl-6-octen-1-yn-3-ol gives citral (as a 1:3 mixture of neral and geranial) in almost quantitative yield. Unfortunately, the scope of this process is restricted to acid-insensitive substrates. Ethynyl-β-ionol does not afford β-ionylideneacetaldehyde, a versatile C_{15}-building block; rather, it decomposes after dehydration to give the corresponding trienyne (Scheme 1).



Scheme 1. The reaction of an acid-insensitive substrate affords the α,β-unsaturated aldehyde, whereas an acid-sensitive substrate, ethynyl-β-ionol, does not.

The most straightforward route to β-ionylideneacetaldehyde (again obtained as a mixture of geometrical isomers[3]) is based on the addition of (*Z*)-2-ethoxyvinyllithium[4] to β-ionone and the subsequent hydrolysis of the resulting (*Z*)-2-ethoxyvinyl-β-ionol under acidic conditions. However, from an economic point of view, it would be attractive to avoid the expensive organometallic reagent and to apply a two-step sequence starting with the ethynylation of β-ionone, followed by the addition of ethanol onto the triple bond of the resulting ethynyl-β-ionol (Scheme 2). However, this goal can be achieved only indirectly.



Scheme 2. Possibilities for the synthesis of β-ionylideneacetaldehyde.

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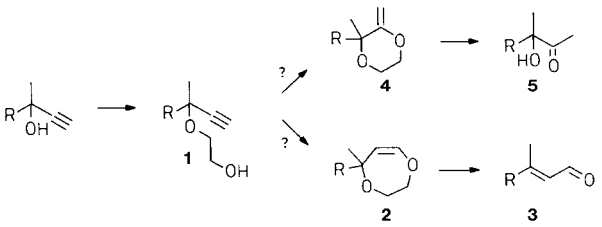
Results and Discussion

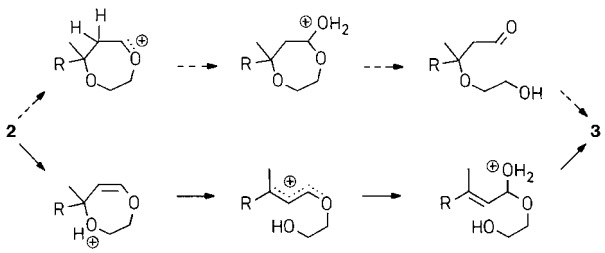
Despite numerous attempts, we did not succeed in achieving a direct conversion of ethynyl-β-ionol into the enether under acceptable conditions. The base-catalyzed addition of methanol or ethanol to triple bonds is known, but it is restricted to acetylene itself and derivatives thereof endowed with activating, that is carbanion-stabilizing, substituents (such as ethynylbenzene or propiolic acid esters).[5]

If an intermolecular reaction fails, the entropy-conserving intramolecular version may offer a better chance. By combining various 1-alkyn-3-ols with oxirane or, more conveniently, ethylene sulfite we prepared a series of ethylene glycol monoethers **1**. The question was now whether the base-catalyzed cyclization, if it occurred at all, would choose the desired course leading to dihydro-1,4-dioxepins **2** or take the wrong track and give methylene-1,4-dioxanes **4**. Depending on the intermediate, acid-promoted hydrolysis would afford enals **3** or hydroxyketones **5** (Scheme 3).



Scheme 3. Possible intramolecular base-catalyzed cyclization reactions of ethylene glycol monoethers **1**.

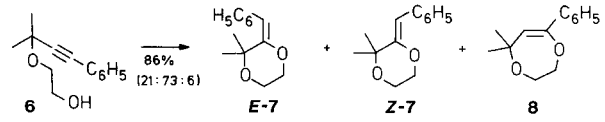
The predicted outcome is based on the assumption that in either case the hydrolysis involves as the key intermediate a (2-hydroxyethyloxy)allyl cation, which is formed by the heterolytic scission of the bond between the tertiary carbon atom and the protonated oxygen atom attached to it (as exemplified for the dioxepins **2** in Scheme 4). If instead the β-carbon atom of the enether unit were preferentially protonated, the hydrolysis of dioxepins **2** and methylenedioxanes **4** would provide 3-(2-hydroxyethoxy)-substituted aldehydes and 2-alkanones, respectively. At least in the latter case, a subsequent elimination of ethylene glycol to produce enones would be extremely difficult to accomplish.



Scheme 4. Possible rearrangements of the key intermediate, the (2-hydroxyethyloxy)allyl cation, produced during hydrolysis.

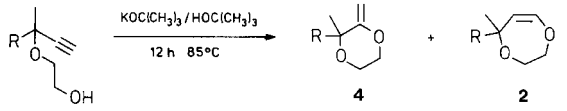
Abstract in German: *3-Hydroxy-1-alkine lassen sich auf einfache Weise in 2-Alkenale umwandeln. Das dreistufige Verfahren besteht aus der Herstellung von 2-Propinylethylenglykolmonoethern **1**, deren basekatalysierter Cyclisierung zu Dihydro-1,4-dioxepinen **2** und deren säurekatalysierter Hydrolyse. Die Methode kann auf wertvolle Zwischenstufen der Isoprenoid-Synthese, etwa auf Ethinyl-β-ionol, erfolgreich angewendet werden.*

The few literature precedents found were anything but encouraging. Ethylene glycol monoethers derived from 2-propyn-1-ol (propargyl alcohol), 2-butyn-1-ol, and 3-butyn-2-ol gave upon cyclization mainly five- and six-membered and only minor amounts of seven-membered rings (yields averaging 5% except in two cases when 15% and 29% were reached).[6] The first example we studied appeared to confirm this trend. When dissolved in a mixture of potassium *tert*-butoxide and *tert*-butyl alcohol and heated under reflux, 2-[(1,1-dimethyl-3-phenyl-2-propynyl)oxy]ethanol (**6**) rapidly reacted to give a mixture of (*Z*)- and (*E*)-3-benzylidene-2,2-dimethyl-1,4-dioxane (**7**; 81%) along with a small quantity of 3,5-dihydro-5,5-dimethyl-7-phenyl-2*H*-1,4-dioxepin (**8**; 5%) (Scheme 5). To our delight, the regioselectivity of the intramolecular addition of the alcohol to a triple bond changed profoundly when we used starting materials **1** which carry no substituent at the terminal acetylenic position. The dioxepins **2** now became the predominant products (Table 1).



Scheme 5. Reaction of 2-[(1,1-dimethyl-3-phenyl-2-propynyl)oxy]ethanol (**6**) to give dioxane **7** and a small quantity of dioxepin **8**.

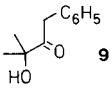
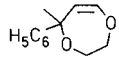
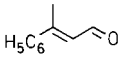
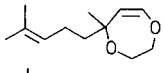
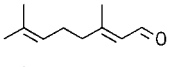
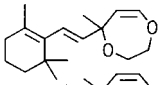
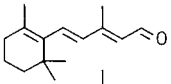
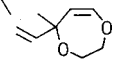
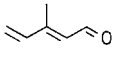
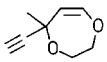
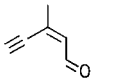
Table 1. Base-catalyzed cyclization of 2-[(1-R-1-methyl-2-propynyl)oxy]ethanols **1**: total yields of products and ratios of six- versus seven-membered rings (**4** vs. **2**) formed.



R	Cpd.	Yield	Ratio **4**/**2**
H_3C	**a**	88%	20 : 80
H_5C_6	**b**	92%	9 : 91
$(H_3C)_2C{=}CH{-}CH_2{-}CH_2{-}$	**c**	94%	15 : 85
	**d**	95%	4 : 96
$H_2C{=}CH{-}$	**e**	86%	7 : 93
$HC{\equiv}C{-}$	**f**	72%	16 : 84

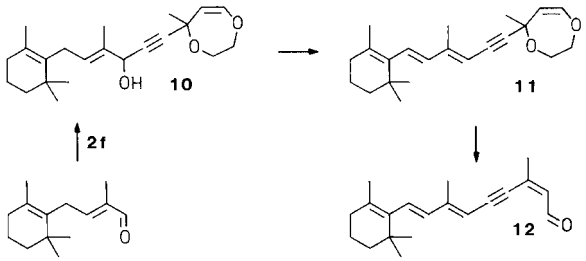
The acid-catalyzed hydrolysis was accomplished with a 1M solution of hydrogen chloride in 20% aqueous tetrahydrofuran (5 h under reflux) and proceeded as expected. The dioxane **7** gave the 3-hydroxy-2-alkanone **9**, while enals **3a–f** were obtained from the dioxepins **2a–f** (Table 2). In general, the

Table 2. Products formed upon acidic hydrolysis of dioxane **7** and dioxepins **2a–f**: yields and, where applicable, *Z/E* ratios.

Cyclic enether	Hydrolysis product	Yield	(*Z*/*E*) ratio
 **7**	 **9**	76%	-
 **2a**	 **3a**	45%	-
 **2b**	 **3b**	65%	25 : 75
 **2c**	 **3c**	40%	33 : 67
 **2d**	 **3d**	90%	25 : 75
 **2e**	 **3e**	45%	33 : 67
 **2f**	 **3f**	50%	87 : 13

products were isolated as a mixture of *Z* and *E* isomers in ratios ranging from 1:2 to 1:3. 3-Methyl-2-penten-4-ynal (**3f**) was the only exception. In agreement with the thermodynamic preference of simple 2-alken-4-ynes[7] for the *cis* configuration, its *Z* isomer was found to predominate.

The 3,5-dihydro-5-ethynyl-5-methyl-2*H*-1,4-dioxepin (**2f**) can be used as an unorthodox[8] isoprenoid C_6 unit. After deprotonation (with butyllithium) to the corresponding lithium acetylide, it was added to the C_{14} aldehyde (*E*)-2-methyl-4-(2,6,6-trimethyl-1-cyclohexenyl)-2-butenal, the cornerstone of Isler's synthesis of vitamin A.[9] Alcohol **10** (obtained in 91% yield) was then submitted to consecutive dehydration (to dioxepin **11**) and hydrolysis to afford 11,12-dehydroretinal **12** (62%; $(Z)^{\Delta 13}/(E)^{\Delta 13}$ 4:1) (Scheme 6).



Scheme 6. Synthesis of 11,12-dehydroretinal (**12**).

Experimental Section

General: For standard working practice and abbreviations see recent publications from this laboratory (e.g. ref. [10]). ^{1}H NMR spectra were recorded at 400 MHz in deuterochloroform.

Preparation of 2-[(2-propynyl)oxy]ethanols 1 and 6:

2-[(1,1-Dimethyl-2-propynyl)oxy]ethanol (**1a**): B.p. 78–80 °C/20 mmHg (ref. [11]: b.p. 171–172 °C); $n_D^{20} = 1.4524$.

2-[(1-Methyl-1-phenyl-2-propynyl)oxy]ethanol (**1b**): Sodium hydride (0.72 g, 30 mmol) was added to a solution of 2-phenyl-3-butyn-2-ol (3.7 g, 25 mmol) in dimethylformamide (0.10 L) at 0 °C. After the evolution of hydrogen had ceased, ethylene sulfite (2.3 mL, 3.3 g, 30 mmol) was added at 0 °C and the mixture was then stirred for 1 h at 0 °C. Diethyl ether (0.10 L) and water (0.10 L) were added and the aqueous layer extracted with diethyl ether (3 × 0.10 L). The combined organic phases were washed with water (3 × 50 mL) and brine (0.10 L), then dried. After evaporation of the solvent, the residue was distilled to give a colorless liquid. Yield: 11.0 g (55%); b.p. 90–92 °C/0.07 mmHg; $d_4^{20} = 1.05$; $n_D^{20} = 1.5245$; ^{1}H NMR: $\delta =$ 7.6 (m, 2H), 7.4 (m, 2H), 7.3 (m, 1H), 3.7 (m, 3H), 3.3 (m, 1H), 2.75 (s, 1H), 2.08 (br s, 1H), 1.77 (s, 3H); MS: 175 (48%, $[M^+ - 15]$), 146 (9%), 129 (100%), 105 (48%); anal. calcd for $C_{12}H_{14}O_2$ (190.24): C 75.76, H 7.42; found C 75.67, H 7.19%.

2-[(1,5-Dimethyl-1-ethynyl-4-hexenyl)oxy]ethanol (**1c**): Prepared as described for **1b** from 3,7-dimethyloct-6-en-1-yn-3-ol (4.3 mL, 3.8 g, 25 mmol). Yield: 1.8 g (37%); b.p. 83–85 °C/0.2 mmHg (ref. [12]: b.p. 85–92 °C/0.4 mmHg); $d_4^{20} = 0.96$; $n_D^{20} = 1.4706$ (ref. [12]: $n_D^{20} = 1.4712$); ^{1}H NMR: $\delta = 5.1$ (m, 1H), 3.7 (m, 4H), 2.47 (s, 1H), 2.1 (m, 2H), 2.03 (s, 1H), 1.7 (m, 2H), 1.68 (d, $J = 0.9$ Hz, 3H), 1.62 (s, 3H), 1.44 (s, 3H); MS: 197 (11%, $[M^+ + 1]$), 119 (100%); anal. calcd for $C_{12}H_{20}O_2$ (196.29): C 73.43, H 10.27; found C 73.47, H 10.07%.

2-[[1-Ethynyl-1-methyl-3-(2,6,6-trimethylcyclohexenyl)-2-propenyl]oxy]-ethanol (**1d**): Due to the instability of the substrate in the presence of bases, in particular sodium hydride, at 0 °C, the standard protocol (see preparation of compound **1b**, above) had to be modified: at −75 °C, butyllithium (25 mmol) in hexane (17 mL) and ethylene sulfite (1.9 mL, 2.7 g, 25 mmol) were consecutively added to ethynyl-β-ionol (5.8 mL, 5.5 g, 25 mmol) in a mixture of diethyl ether (0.10 L) and hexamethylphosphoric triamide (9.0 mL, 8.2 g, 50 mmol). The solution was kept at −75 °C for 1 h and then allowed to warm to 25 °C. Water (0.10 L) was added and the product was extracted with diethyl ether (3 × 0.10 L). After evaporation of the solvent, the residue was eluted from silica gel with a mixture of ethyl acetate and hexanes [1:4 (*v*/*v*)] to afford a colorless oil. Yield: 3.1 g (47%); $d_4^{20} = 1.03$; $n_D^{20} = 1.4950$; ^{1}H NMR: $\delta = 6.45$ (dm, $J = 16.0$ Hz, 1H), 5.33 (d, $J = 16.0$ Hz, 1H), 3.7 (m, 3H), 3.5 (m, 1H), 2.63 (s, 1H), 2.0 (m, 1H), 1.98 (t, $J = 6.3$ Hz, 2H), 1.66 (d, $J = 0.9$ Hz, 3H), 1.61 (s, 3H), 1.6 (m, 2H), 1.5 (m, 2H), 1.01 (s, 3H), 0.99 (s, 3H); MS: 263 (8%, $[M^+ + 1]$), 262 (23%, $[M^+]$), 247 (100%); anal. calcd for $C_{17}H_{26}O_2$ (262.39): C 77.82, H 9.99; found C 78.03, H 9.84%.

2-[(1-Ethynyl-1-methyl-2-propenyl)oxy]ethanol (**1e**): Prepared as described for **1b** from 3-methylpent-1-en-4-yn-3-ol (2.8 mL, 2.4 g, 25 mmol). Yield: 2.1 g (60%); b.p. 59–60 °C/3 mmHg; $d_4^{20} = 0.97$; $n_D^{20} = 1.4571$; ^{1}H NMR: $\delta = 5.75$ (dd, $J = 17.2$, 10.2 Hz, 1H), 5.59 (br d, $J = 17.2$ Hz, 1H), 5.27 (br d, $J = 10.2$ Hz, 1H), 3.7 (m, 2H), 3.6 (m, 1H), 3.5 (m, 1H), 2.61 (s, 1H), 2.05 (br s, 1H), 1.57 (s, 1H); MS: 141 (1%, $[M^+ + 1]$), 140 (3%, $[M^+]$), 125 (100%); anal. calcd for $C_8H_{12}O_2$ (140.18): C 68.55, H 8.63; found C 68.50, H 8.54%.

2-[(1-Ethynyl-1-methyl-2-propynyl)oxy]ethanol (**1f**): Analogously obtained from 3-methylpent-1,4-diyn-3-ol[13] (2.4 g, 25 mmol). Yield: 2.1 g (60%); b.p. 60–61 °C/2 mmHg; $d_4^{20} = 0.98$; $n_D^{20} = 1.4605$; ^{1}H NMR: $\delta = 3.9$ (m, 2H), 3.8 (m, 2H), 2.57 (s, 2H), 2.0 (br s, 1H), 1.81 (s, 3H); MS: 123 (25%, $[M^+ - 15]$), 107 (14%), 77 (100%); anal. calcd for $C_8H_{10}O_2$ (138.17): C 69.55, H 7.29; found C 69.60, H 7.39%.

2-[(1,1-Dimethyl-3-phenyl-2-propenyl)oxy]ethanol (**6**): A mixture containing 2-[(1,1-dimethylprop-2-ynyl)oxy]ethanol[11] (3.4 mL, 3.2 g, 25 mmol), bromobenzene (4.0 mL, 5.9 g, 38 mmol), tetrakis(triphenylphospine)palladium (65 mg, 0.056 mmol), copper bromide (28 mg, 0.20 mmol), lithium bromide (90 mg, 1.00 mmol), and piperidine (20 mL) was heated to 90 °C with stirring. When the exothermic reaction (which raised the temperature temporarily to about 110 °C) had ceased, the mixture was heated to 100 °C for an additional 30 min. Water (0.10 L) was added and the product then extracted with diethyl ether (4 × 0.10 L). The combined organic layers were dried and evaporated. Distillation of the residue gave a colorless liquid. Yield: 4.8 g (86%); b.p. 98–100 °C/0.3 mmHg; $d_4^{20} = 1.04$; $n_D^{20} = 1.5353$; ^{1}H NMR: $\delta = 7.4$ (m, 2H), 7.3 (m, 2H), 3.8 (m, 4H), 1.61 (s, 1H), 1.56 (s, 6H); MS: 205 (2%, $[M^+ + 1]$), 204 (1%, $[M^+]$), 160 (52%), 143 (100%); anal. calcd for $C_{13}H_{16}O_2$ (204.27): C 76.44, H 7.89; found C 76.51, H 8.04%.

Dioxepins and dioxanes:

(*Z*)-3-Benzylidene-2,2-dimethyl-1,4-dioxane [(*Z*)-**7**]: A solution of 2-[(1,1-dimethyl-3-phenyl-2-propynyl)oxy]ethanol (**6**; 4.9 mL, 5.1 g, 25 mmol) in *tert*-butyl alcohol (5 mL) was added dropwise to a boiling solution of potassium *tert*-butoxide (2.8 g, 25 mmol) in *tert*-butyl alcohol (20 mL). The solution was heated under reflux for 12 h. Water (0.10 L) was added and the product then extracted with diethyl ether (3 × 0.10 L), dried, and the

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solvent evaporated. Distillation gave a liquid product which, according to gas chromatography (30 m, DB-1, 100 °C; 30 m, DB-WAX, 100 °C), contained the dioxanes (*Z*)-**7** and (*E*)-**7** along with the dioxepin **8** in a 73:21:6 ratio. Yield: 4.2 g (83 %); b.p. 81–82 °C/0.2 mmHg; anal. calcd for $C_{13}H_{16}O_2$ (204.27): C 76.44, H 7.89; found C 76.36, H 7.85. (*Z*)-3-Benzylidene-2-dimethyl-1,4-dioxane [(*Z*)-**7**] was isolated as a pure compound by preparative gas chromatography (6 m, 5 % C-20 M, 50 °C); $n_D^{20} = 1.5526$; ^{1}H NMR: $\delta = 7.6$ (m, 2H), 7.3 (m, 2H), 7.2 (m, 1H), 5.62 (s, 1H), 4.1 (m, 2H), 3.9 (m, 2H), 1.52 (s, 6H); MS: 205 (100 %, $[M^+ + 1]$), 204 (7 %, $[M^+]$), 189 (12 %, $[M^+ - 15]$). The structures of the two other products, (*E*)-3-benzylidene-2,2-dimethyl-1,4-dioxane [(*E*)-**7**] and 2,3-dihydro-5,5-dimethyl-7-phenyl-1,4-dioxepin (**8**), obtained by preparative gas chromatography (see above) as a 2:1 mixture, were tentatively assigned on the basis of their ^{1}H NMR spectra: $\delta = 7.6$ (m, 2H), 7.3 (m, 2H), 7.2 (m, 1H), 6.21 (s, 0.67H), 5.32 (s, 0.33H), 4.2 (m, 0.67H), 4.0 (m, 2H), 3.9 (m, 1.33H), 1.47 (s, 2H), 1.27 (s, 4H).

2,3-Dihydro-5,5-dimethyl-1,4-dioxepin (**2a**): An analogous reaction performed with 2-[(1,1-dimethyl-2-propynyl)oxy]ethanol (**1a**; 3.4 mL, 3.2 g, 25 mmol) gave an 80:20 mixture of dioxepin **2a** and dioxane **4a**; yield: 2.6 g (81 %); b.p. 68–70 °C/65 mmHg. The two components were separated by preparative gas chromatography (6 m, 5 % C-20 M, 50 °C). **Dioxepin 2a**: $d_4^{20} = 0.88$; $n_D^{20} = 1.4475$; ^{1}H NMR: $\delta = 5.99$ (d, $J = 8.3$ Hz, 1H), 4.36 (d, $J =$ 8.3 Hz, 1H), 4.1 (m, 2H), 3.9 (m, 2H), 1.33 (s, 6H); MS: 129 (100 %, $[M^+ + 1]$), 128 (2 %, $[M^+]$), 118 (46 %); anal. calcd for $C_7H_{12}O_2$ (128.17): C 65.60, H 9.44; found C 65.61, H 9.47 %. **2,2-Dimethyl-3-methylene-1,4-dioxane** (**4a**): ^{1}H NMR: $\delta = 4.42$ (d, $J = 1.2$ Hz, 1H), 4.28 (d, $J = 1.2$ Hz, 1H), 3.9 (m, 2H), 3.8 (m, 2H), 1.42 (s, 6H); MS: 129 (100 %, $[M^+ + 1]$), 128 (3 %, $[M^+]$), 113 (56 %); anal. calcd for $C_7H_{12}O_2$ (128.17): C 65.60, H 9.44; found C 65.56, H 9.29 %.

2,3-Dihydro-5-methyl-5-phenyl-1,4-dioxepin (**2b**): Under the same conditions as described for the reaction of **6**, 2-[(1-methyl-1-phenyl-2-propynyl)oxy]ethanol (**1b**; 4.8 mL, 4.8 g, 25 mmol) gave a 91:9 mixture of dioxepin **2b** and dioxane **4b**. Yield: 4.1 g (86 %); b.p. 69–70 °C/0.25 mmHg. The two components were separated by preparative gas chromatography (6 m, 5 % C-20 M, 150 °C). **Dioxepin 2b**: $d_4^{20} = 0.91$; $n_D^{20} = 1.5379$; ^{1}H NMR: $\delta = 7.5$ (m, 2H), 7.3 (m, 2H), 7.2 (m, 1H), 6.27 (d, $J = 8.3$ Hz, 1H), 4.81 (d, $J = 8.3$ Hz, 1H), 4.11 (ddd, $J = 12.7$, 5.2, 1.3 Hz, 1H), 4.02 (ddd, $J = 12.7$, 7.8, 1.6 Hz, 1H), 3.77 (ddd, $J = 14.1$, 5.2, 1.6 Hz, 1H), 3.55 (ddd, $J = 14.1$, 7.8, 1.3 Hz, 1H), 1.59 (s, 3H); MS: 191 (10 %, $[M^+ + 1]$), 190 (2 %, $[M^+]$), 118 (100 %); anal. calcd for $C_{12}H_{14}O_2$ (190.24): C 75.76, H 7.42; found C 75.54, H 7.35 %. **2-Methyl-3-methylene-2-phenyl-1,4-dioxane** (**4b**): ^{1}H NMR: $\delta = 7.5$ (m, 2H), 7.4 (m, 2H), 7.3 (m, 1H), 4.85 (d, $J = 1.2$ Hz, 1H), 4.58 (d, $J = 1.2$ Hz, 1H), 3.99 (ddd, $J = 12.2$, 11.0, 3.4 Hz, 1H), 3.85 (ddd, $J = 12.2$, 2.9, 2.1 Hz, 1H), 3.80 (ddd, $J = 11.9$, 11.0, 2.9 Hz, 1H), 3.62 (ddd, $J = 11.9$, 3.4, 2.1 Hz, 1H), 1.57 (s, 3H); MS: 191 (8 %, $[M^+ + 1]$), 190 (53 %, $[M^+]$), 105 (100 %); anal. calcd for $C_{12}H_{14}O_2$ (190.24): C 75.76, H 7.42; found C 75.71, H 7.46 %.

2,3-Dihydro-5-methyl-5-(4-methyl-3-pentenyl)-1,4-dioxepin (**2c**): Under the same conditions as described for the reaction of **6**, 2-[(1,5-dimethyl-1-ethynyl-4-hexenyl)oxy]ethanol (**1c**; 5.1 mL, 4.9 g, 25 mmol) gave an 85:15 mixture of dioxepin **2c** and dioxane **4c**. Yield: 4.3 g (87 %). The two components were separated by column chromatography (silica gel, ethyl acetate/hexanes 1:6). **Dioxepin 2c**: b.p. 58 –59 °C/0.5 mmHg; $d_4^{20} = 0.89$; $n_D^{20} = 1.4768$; ^{1}H NMR: $\delta = 6.04$ (d, $J = 8.5$ Hz, 1H), 5.1 (m, 1H), 4.24 (d, $J = 8.5$ Hz, 1H), 4.13 (ddd, $J = 12.5$ Hz, 5.5 Hz, 1.1 Hz, 1H), 4.04 (ddd, $J =$ 12.5, 6.8, 1.1 Hz, 1H), 3.88 (ddd, $J = 14.2$, 6.8, 1.1 Hz, 1H), 3.80 (ddd, $J =$ 14.2, 5.5, 1.1 Hz, 1H), 2.1 (m, 2H), 1.68 (d, $J = 1.2$ Hz, 3H),1.61 (s, 1H), 1.5 (m, 2H), 1.28 (s, 3H); MS: 197 (19 %, $[M^+ + 1]$), 196 (2 %, $[M^+]$), 119 (100 %); anal. calcd for $C_{12}H_{20}O_2$ (196.29): C 73.43, H 10.27; found C 73.29, H 10.07 %. **3-Methyl-3-methylene-2-(4-methyl-3-pentenyl)-1,4-dioxane** (**4c**)**:** b.p. 59–60 °C/0.5 mmHg; $n_D^{20} = 1.4723$; ^{1}H NMR: $\delta = 5.1$ (m, 1H), 4.46 (d, $J = 1.4$ Hz, 1H), 4.23 (d, $J = 1.4$ Hz, 1H), 2.9 (m, 3H), 3.7 (m, 1H), 2.0 (m, 2H), 1.9 (m, 1H), 1.68 (d, $J = 0.9$ Hz, 3H), 1.7 (m, 1H), 1.61 (br s, 3H), 1.36 (s, 3H); MS: 197 (17 %, $[M^+ + 1]$), 196 (1 %, $[M^+]$), 119 (100 %); anal. calcd for $C_{12}H_{20}O_2$ (196.29): C 73.43, H 10.27; found C 73.33, H 10.11 %.

2,3-Dihydro-5-methyl-5-[2-(2,6,6-trimethylcyclohexenyl)ethenyl]-1,4-dioxepin (**2d**): Under the same conditions as described for the reaction of **6**, 2-[[1-ethynyl-1-methyl-3-(2,6,6-trimethylcyclohexenyl)-2-propenyl]oxy]ethanol (**1d**; 6.3 mL, 6.5 g, 25 mmol) gave a 96:4 mixture of **2d** and **4d**. Yield: 7.2 g (79 %); b.p. 85–87 °C/0.02 mmHg; $d_4^{20} = 0.90$; $n_D^{20} = 1.4706$. No separation of the two isomers was achieved. **Dioxepin 2d**: ^{1}H NMR: $\delta =$ 6.21 (d, $J = 8.3$, 1H), 6.11 (dm, $J = 16.2$ Hz, 1H), 5.32 (d, $J = 16.2$ Hz, 1H), 4.43 (d, d $J = 8.3$ Hz, 1H), 4.20 (ddd, $J = 12.5$, 4.2, 0.7 Hz, 1H), 3.99 (ddd, $J = 12.5$, 8.6, 1.1 Hz, 1H), 3.90 (ddd, $J = 14.0$, 8.6, 0.7 Hz, 1H), 3.75 (ddd, $J = 14.0$, 4.2, 0.7 Hz, 1H), 1.98 (t, $J = 6.2$ Hz, 2H), 1.66 (d, $J = 0.9$ Hz, 3H),1.6 (m, 2H), 1.4 (m, 2H), 1.42 (s, 3H), 0.99 (s, 6H); MS: 263 (32 %, $[M^+ + 1]$), 262 (37 %, $[M^+]$), 247 (100 %); anal. calcd for $C_{17}H_{26}O_2$ (262.39): C 77.82, H 9.99; found C 78.22, H 10.13 %. **2-Methyl-3-methylene-2-[2-(2,6,6-trimethylcyclohex-1-en-1-yl)-1-ethylenyl]-1,4-dioxane** (**4d**): The by-product was identified by gas chromatography (30 m, DB-1, 180 °C; 30 m, DB-WAX, 180 °C) and its structure assigned on the basis of its characteristic olefinic ^{1}H NMR signals: $\delta = 4.51$ (d, $J = 1.2$ Hz, 0.04H), 4.36 (d, $J =$ 1.2 Hz, 0.04H).

2,3-Dihydro-5-ethylenyl-5-methyl-1,4-dioxepin (**2e**) and **2-ethenyl-2-methyl-3-methylene-1,4-dioxane** (**4e**)**:** Under the same conditions as described for the reaction of **6**, 2-[(1-ethynyl-1-methyl-2-propenyl)oxy]ethanol (**1e**; 3.6 mL, 3.5 g, 25 mmol) gave a 93:7 mixture of dioxepin **2e** and dioxane **4e**. Yield: 2.8 g (80 %); b.p. 73–74 °C/38 mmHg; $d_4^{20} = 0.89$; $n_D^{20} = 1.4650$; ^{1}H NMR: $\delta = 6.18$ (d, $J = 8.5$ Hz, 0.9H), 5.87 (dd, $J = 17.6$, 10.5 Hz, 0.1H), 5.76 (dd, $J = 17.3$, 10.4 Hz, 0.9H), 5.3 (m, 0.2H), 5.28 (dd, $J = 17.3$, 1.5 Hz, 0.9H), 5.17 (dd, $J = 10.4$, 1.5 Hz, 0.9H), 4.61 (d, $J = 1.2$ Hz, 0.1H), 4.35 (d, $J =$ 8.5 Hz, 0.9H), 4.34 (d, $J = 1.2$ Hz, 0.1H), 4.16 (ddd, $J = 12.6$, 4.3, 1.2 Hz, 1.0H), 4.00 (ddd, $J = 12.6$, 8.1, 1.5 Hz, 1H), 3.82 (ddd, $J = 14.0$, 8.5, 1.2 Hz, 1H), 3.73 (ddd, $J = 14.0$, 4.3, 1.5 Hz, 1H), 1.43 (s, 0.3H), 1.38 (s, 2.7H); MS: 141 (1 %, $[M^+ + 1]$), 140 (4 %, $[M^+]$), 126 (50 %), 125 (100 %); anal. calcd for $C_8H_{12}O_2$ (140.18): C 68.55, H 8.63; found C 68.94, H 8.64 %.

2,3-Dihydro-5-ethynyl-5-methyl-1,4-dioxepin (**2f**): Under the same conditions as described for the reaction of **6**, 2-[(1-ethynyl-1-methyl-2-propenyl)oxy]ethanol (**1f**; 3.6 mL, 3.5 g, 25 mmol) gave a 73:27 mixture of dioxepin **2f** and dioxane **4f**. Yield: 2.2 g (65 %). The two isomers were separated by column chromatography (silica gel, ethyl acetate/hexanes 1:1 (*v*/*v*)). **Dioxepin 2f**: B.p. 50–53 °C/20 mmHg; $n_D^{20} = 1.4727$; ^{1}H NMR: $\delta =$ 6.11 (d, $J = 7.9$ Hz, 1H), 4.55 (d, $J = 7.9$ Hz, 1H), 4.33 (ddd, $J = 12.9$, 4.3, 1.2 Hz, 1H), 4.21 (ddd, $J = 13.9$, 8.2, 1.2 Hz, 1H), 3.99 (ddd, $J = 12.9$, 8.2, 1.5 Hz, 1H), 3.91 (ddd, $J = 13.9$, 4.3, 1.5 Hz, 1H), 2.50 (s, 1H), 1.38 (s, 3H); MS: 139 (1 %, $[M^+ + 1]$), 138 (2 %, $[M^+]$), 105 (100 %); anal. calcd for $C_8H_{10}O_2$ (138.17): C 69.55, H 7.29; found C 69.60, H 7.39 %. **2-Ethynyl-2-methyl-3-methylene-1,4-dioxane** (**4f**): b.p. 50–51 °C/20 mmHg; $n_D^{20} =$ 1.4736; ^{1}H NMR: $\delta = 4.57$ (d, $J = 1.6$ Hz, 1H), 4.52 (d, $J = 1.6$ Hz, 1H), 4.38 (ddd, $J = 14.2$, 11.1, 3.1 Hz, 1H), 4.02 (ddd, $J = 11.1$, 2.8, 1.8 Hz, 1H), 3.92 (ddd, $J = 14.2$, 11.6, 3.1 Hz, 1H), 3.73 (ddd, $J = 11.6$, 2.8, 1.8 Hz, 1H), 2.56 (s, 1H), 1.67 (s, 3H); MS: 139 (1 %, $[M^+ + 1]$), 138 (2 %, $[M^+]$), 105 (100 %); anal. calcd for $C_8H_{10}O_2$ (138.17): C 69.55, H 7.29; found C 69.60, H 7.39 %. Heating a mixture of 2-[(1-ethynyl-1-methyl-2-propenyl)oxy]ethanol (3.6 mL, 3.5 g, 25 mmol), potassium hydroxide (2.0 g, 50 mmol) and water (25 mL) for 3 h under reflux gave an 84:16 mixture of dioxepin **2f** and dioxane **4f**. Yield: 2.5 g (72 %).

Hydrolysis of dioxanes (7) and dioxepins (2):

3-Hydroxy-3-methyl-1-phenyl-2-butanone (**9**): A solution of 3-benzylidene-2,2-dimethyl-1,4-dioxane (**7**; *Z*/*E* ratio = 78:22; 5.1 mL, 5.1 g, 25 mmol), which also contained 6 % of dioxepin **8**), and 12 M sulfuric acid (20 mL) in tetrahydrofuran (0.10 L) was kept at 25 °C for 12 h. Water (50 mL) was added and the product then extracted with diethyl ether (4 × 50 mL). The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate (2 × 50 mL) and brine (50 mL), and then dried. After evaporation of the solvent, the residue was distilled to give α-hydroxyketone **9**. Yield: 3.4 g (76 %); b.p. 96–99 °C/0.02 mmHg; (ref. [14]: b.p. 100 °C/0.05 mmHg); $n_D^{20} = 1.5454$; ^{1}H NMR: $\delta =$ 7.3 (m, 5H), 3.87 (s, 2H), 1.8 (br s, 1H), 1.43 (s, 6H).

3-Methyl-3-butenal (**3a**): A solution of 2,3-dihydro-5-dimethyl-1,4-dioxepin (**2a**; 3.6 mL, 3.2 g, 25 mmol) and 6 M hydrochloric acid (20 mL) in tetrahydrofuran (0.10 L) was heated under reflux for 5 h. Water (50 mL) was added and the product was then extracted with diethyl ether (4 × 50 mL). The combined organic layers were washed with a saturated aqueous solution of sodium hydrogen carbonate (2 × 50 mL) and brine (50 mL), and then dried. Distillation afforded the α,β-unsaturated aldehyde **3a**. Yield: 0.95 g (45 %); b.p. 75–77 °C/70 mmHg (ref. [15]: b.p. 130–135 °C); $n_D^{20} = 1.4550$ (ref. [15]: $n_D^{20} = 1.4550$); ^{1}H NMR: $\delta = 9.96$ (d, $J =$ 8.2 Hz, 1H), 5.89 (dm, $J = 8.2$ Hz, 1H), 2.17 (d, $J = 1.2$ Hz, 3H), 1.99 (d, $J = 1.1$ Hz, 3H).

(*E*)-3-Phenyl-2-butenal (**3b**): From 2,3-dihydro-5-methyl-5-phenyl-1,4-dioxepin (**2b**; 5.2 mL, 4.8 g, 25 mmol), as described for the hydrolysis of dioxepin **2a**, as a 1:3 *Z*/*E* mixture according to gas chromatography (30 m, DB-1, 100 °C; 5 m, 5% C-20M, 150 °C). Yield: 2.4 g (65%); b.p. 75–77 °C/0.5 mmHg (ref. [16]: b.p. 79–84 °C/0.1 mmHg); $n_D^{20} = 1.5866$ (ref. [16]: $n_D^{20} = 1.5861$).

(*E*)-3,7-Dimethyl-2,6-octadienal (**3c**): From 2,3-dihydro-5-methyl-5-(4-methyl-3-pentenyl)-1,4-dioxepin (**2c**; 5.5 mL, 4.9 g, 25 mmol), as described for the hydrolysis of dioxepin **2a**, as a 1:2 *Z*/*E* mixture according to gas chromatography (30 m, DB-1, 100 °C; 30 m, DB-WAX, 120 °C). Yield: 1.5 g (40%); b.p. 58–60 °C/1 mmHg (ref. [17]: b.p. 53–54 °C/0.05 mmHg); $n_D^{20} = 1.4870$ (ref. [18]: $n_D^{20} = 1.4874$).

(2(*E*),4(*E*))-3-Methyl-5-(2,6,6-trimethylcyclohex-1-enyl)pent-2,4-dien-1-al (**3d**): From 2,3-dihydro-5-methyl-5-[2-(2,6,6-trimethylcyclohexenyl)ethenyl]-1,4-dioxepin (**2d**; 7.3 mL, 6.6 g, 25 mmol), as described for the hydrolysis of dioxepin **2a**, as a 1:3 2(*Z*),4(*E*)/2(*E*),4(*E*) mixture according to gas chromatography (30 m, DB-1, 180 °C; 30 m, DB-WAX, 180 °C). Yield: 4.9 g (90%); b.p. 95–98 °C/0.05 mmHg (ref. [19]: b.p. 90–95 °C/0.01 mmHg); $n_D^{20} = 1.5765$ (ref. [19]: $n_D^{20} = 1.5780$).

(*E*)-3-Methyl-2,4-pentadienal (**3e**): From 2,3-dihydro-5-ethylenyl-5-methyl-1,4-dioxepin (**2e** containing 7% of dioxane **4e**) (3.9 mL, 3.5 g, 25 mmol), as described for the hydrolysis of dioxepin **2a**, as a 1:2 *Z*/*E* mixture according to gas chromatography (30 m, DB-1, 60 °C; 30 m, DB-WAX, 60 °C). Yield: 1.0 g (45%); b.p. 54–56 °C/12 mmHg (ref. [20]: b.p. 51–52 °C/12 mmHg); $n_D^{20} = 1.5205$ (ref. [20]: $n_D^{20} = 1.5220$).

(*Z*)-3-Methyl-2-penten-4-ynal (**3f**): From 2,3-dihydro-5-ethynyl-5-methyl-1,4-dioxepin (**2f**) (3.8 mL, 3.5 g, 25 mmol), as described for the hydrolysis of dioxepin **2a**, as a 7:1 *Z*/*E* mixture according to gas chromatography (5 m, 5% SE-30, 70 °C; 5 m, 5% C-20M, 70 °C). Yield: 1.2 g (50%); b.p. 47–50 °C/20 mmHg (ref. [21]: b.p. 40–44 °C/14 mmHg); $n_D^{20} = 1.4985$ (ref. [22]: $n_D^{20} = 1.4970$).

11,12-Dehydroretinal

2,3-Dihydro-5-[4(*E*)]-3-hydroxy-4-methyl-6-(2,6,6-trimethylcyclohexen-yl)-4-hexen-1-ynyl]-5-methyl-1,4-dioxepin (**10**): Butyllithium (25 mmol) in hexane (17 mL) and 2-methyl-4-(2,6,6-trimethylcyclohexenyl)-2-butenal[23] (5.5 mL, 5.2 g, 25 mmol) were added consecutively to a solution of 2,3-dihydro-5-ethynyl-5-methyl-1,4-dioxepin (**2f**; 3.8 mL, 3.5 g, 25 mmol) in tetrahydrofuran (0.10 L) cooled to −75 °C. After 1 h at 25 °C, ethanol (10 mL) was added. The mixture was absorbed on silica gel (10 mL) and eluted from a column filled with more silica gel (200 mL) (ethyl acetate/hexanes 1:4 (*v*/*v*)) to afford a 1:2 diastereomeric mixture. Yield: 7.8 g (91%); anal. calcd for $C_{22}H_{32}O_3$ (344.49): C 76.70, H 9.36; found C 76.74, H 9.11%. **Minor diastereoisomer** (isolated from the first chromatographic fractions): $n_D^{20} = 1.4995$; 2.6 g (30%); ^{1}H NMR: $\delta = 6.05$ (d, $J = 8.0$ Hz, 1H), 5.47 (t, $J = 6.5$ Hz, 1H), 4.77 (d, $J = 5.5$ Hz, 1H), 4.53 (d, $J = 8.0$ Hz, 1H), 4.30 (ddm, $J = 12.8$, 4.6 Hz, 1H), 4.16 (ddm, $J = 13.8$, 8.3 Hz, 1H), 3.97 (ddm, $J = 12.8$, 8.3 Hz, 1H), 3.85 (ddm, $J = 13.8$, 4.6 Hz, 1H), 2.74 (d, $J = 6.5$ Hz, 2H), 1.91 (br t, $J = 6.3$ Hz, 2H), 1.80 (s, 3H), 1.61 (s, 3H), 1.6 (m, 2H), 1.57 (s, 3H), 1.4 (m, 2H), 0.97 (s, 3H), 0.96 (s, 3H); MS: 345 (1%, $[M^+ + 1]$), 279 (4%), 207 (6%), 123 (100%). **Major diastereoisomer** (isolated from the later chromatographic fractions): $n_D^{20} = 1.5041$; 5.2 g (61%); ^{1}H NMR: $\delta = =$ 6.05 (d, $J = 7.9$ Hz, 1H), 5.46 (t, $J = 6.5$ Hz, 1H), 4.77 (d, $J = 5.5$ Hz, 1H), 4.53 (d, $J = 7.9$ Hz, 1H), 4.30 (ddm, $J = 12.6$, 4.7 Hz, 1H), 4.16 (ddm, $J = 13.9$, 8.2 Hz, 1H), 3.97 (ddm, $J = 12.6$, 8.2 Hz, 1H), 3.85 (ddm, $J = 13.9$, 4.7 Hz, 1H), 2.74 (d, $J = 6.5$ Hz, 2H), 1.91 (br t, $J = 6.3$ Hz, 2H), 1.80 (s, 3H), 1.6 (m, 2H), 1.57 (s, 3H), 1.53 (s, 3H), 1.4 (m, 2H), 0.97 (s, 3H), 0.96 (s, 3H); MS: 345 (9%, $[M^+ + 1]$), 344 (11%, $[M^+]$), 329 (15%, $[M^+ - 15]$), 327 (100%).

[3(*E*),5(*E*)]-2,3-Dihydro-5-methyl-5-[(4-methyl-6-(2,6,6-trimethylcyclo-hexenyl)-3,5-hexadien-1-ynyl]-1,4-dioxepin (**11**)**:** (Methoxycarbonylsulfamoyl)triethylammonium hydroxide[24] (11.9 g, 50 mmol) and the hydroxylated dioxepin **10** (8.6 mL, 8.6 g, 25 mmol) were dissolved in toluene (0.10 L). After heating to 80 °C for 6 h, the mixture was absorbed on silica gel (10 mL). Column chromatography (ethyl acetate/hexanes 1:10 (*v*/*v*)) afforded a yellow oil. Yield: 5.3 g (65%); $n_D^{20} = 1.5527$; ^{1}H NMR: $\delta = 6.24$ (br d, $J = 16.0$ Hz, 1H), 6.08 (d, $J = 16.0$ Hz, 1H), 6.07 (d, $J = 8.0$ Hz, 1H), 5.44 (br s, 1H), 4.61 (d, $J = 8.0$ Hz, 1H), 4.34 (ddm, $J = 12.8$, 4.6 Hz, 1H), 4.24 (ddm, $J = 14.2$, 8.2 Hz, 1H), 4.00 (ddd, $J = 12.8$, 8.2, 1.4 Hz, 1H), 3.88 (ddd, $J = 14.2$, 4.6, 1.4 Hz, 1H), 2.04 (s, 3H), 2.00 (br t, $J = 6.3$ Hz, 2H,), 1.68 (s, 3H), 1.63 (s, 3H), 1.6 (m, 2H), 1.4 (m, 2H), 1.00 (s, 6H); MS: 327 (70%, $[M^+ + 1]$), 326 (15%, $[M^+]$), 311 (14%, $[M^+ - 15]$), 113 (100%); anal. calcd for $C_{22}H_{30}O_2$ (326.48): C 80.94, H 9.26; found C, 81.10 H 9.36%.

[2(*Z*),6(*E*),8(*E*)]-3,7-Dimethyl-9-(2,6,6-trimethylcyclohexenyl)-2,6,8-nonatrien-4-ynal (**12**):[25,26] A solution of 6 M hydrochloric acid (20 mL) and dioxepin **11** (8.5 mL, 8.2 g, 25 mmol) in tetrahydrofuran (0.10 L) was kept under nitrogen for 16 h at 25 °C. Then diethyl ether (0.10 L) and water (50 mL) were added. The organic layer was washed with an aqueous solution of saturated sodium hydrogencarbonate (2 × 50 mL) and brine (50 mL), and then dried. After evaporation of the solvent, the residue was purified by chromatography (neutral aluminum oxide, ethyl acetate/hexanes 1:10 (*v*/*v*)) to give a yellow oil which, according to gas chromatography (30 m, DB-1, 200 °C; 30 m, DB-WAX, 200 °C), contained the [2(*Z*),6(*E*),8(*E*)] and (2(*E*),6(*E*),8(*E*)] isomers in a 4:1 ratio. Yield: 4.4 g (62%); $n_D^{20} = 1.6094$; ^{1}H NMR: $\delta = 10.08$ (d, $J = 8.3$ Hz, 0.8H), 10.04 (d, $J = 8.3$ Hz, 0.2H), 6.39 (dm, $J = 16.2$ Hz, 1H), 6.16 (d, $J = 16.2$ Hz, 1H), 6.12 (dm, $J = 8.3$ Hz, 1H), 5.62 (br s, 0.8H), 5.60 (br s, 0.2H), 2.35 (d, $J = 1.5$ Hz, 0.6H), 2.17 (d, $J = 1.2$ Hz, 2.4H), 2.11 (d, $J = 1.4$ Hz, 0.6H), 2.13 (d, $J = 0.8$ Hz, 3H), 2.0 (m, 2H), 1.71 (d, $J = 0.7$ Hz, 2.4H), 1.6 (m, 2H), 1.5 (m, 2H), 1.02 (s, 6H).

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