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Synthesis of Analogues of the Mutagenic Sesquiterpenes Isovelleral and Merulidial via Stereoselective Cyclopropanation of Cyclohexenecarbaldehydes

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Abstract: Stereoselective cyclopropanation of 5-acetoxy-6-(diethoxymethyl)-1-cyclohexenecarbaldehyde and its 2-methyl derivative with dimethyl sulfoxonium methylide yielded, after acetal hydrolysis and elimination, bicyclo[4.1.0]hept-2-ene-1,2-dicarbaldehyde and its 6-methyl derivative. The products contain the chemical functionalities that are responsible for the bioactivities of the fungal sesquiterpenes isovelleral and merulidial, and the results presented here indicate that the cyclopropane ring plays a crucial role for the mutagenic activity of these compounds in the Ames' Salmonella assay.

Terpenoids containing a cyclohexene-1,6-dicarbaldehyde functionality and possessing antibiotic and antifeedant activities have been isolated from different natural sources such as plants, insects, marine organisms and fungi. Examples include (see Figure 1) polygodial (**1**),[1] scalaradial (**2**),[2] isovelleral (**3**),[3] marasmic acid (**4**),[4] and merulidial (**5**).[5] Whereas polygodial (**1**) and isovelleral (**3**) possess approximately the same antimicrobial and cytotoxic activities,[6] only the latter is mutagenic, towards both bacteria[7] and mammalian cells.[8]

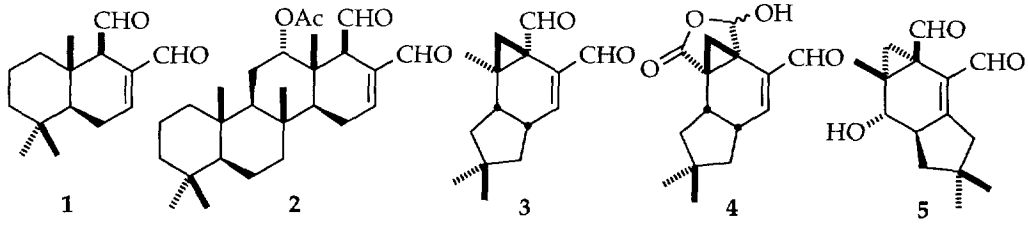


Figure 1.

Marasmic acid (**4**) and merulidial (**5**) are likewise mutagenic, whereas scalaradial (**2**) is not.[7] The possibility for compounds **1-2** to interact with the genetic material may therefore be different compared with compounds **3-5**. In order to study this we needed new derivatives of cyclohexene-1,6-dicarbaldehydes containing a cyclopropane ring adjacent to the saturated aldehyde function. A synthesis of racemic

cyclohexene-1,6-dicarbaldehydes (outlined in Figure 2), by which derivatives substituted at C-2 with an alkyl group can be obtained by using the corresponding furan as the starting material, was recently described.[9]

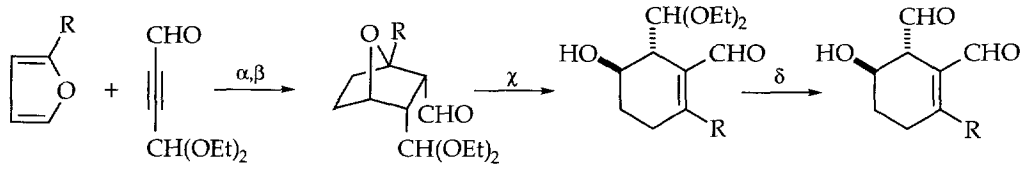
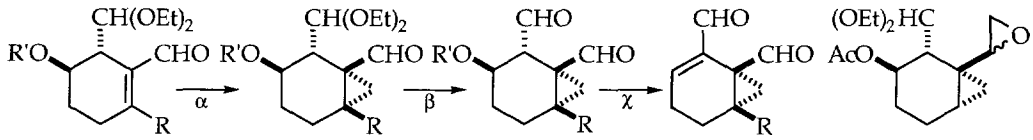


Figure 2. α) 70° C, neat; β) H_2-Pd/C, EtOAc; χ) *t*-BuOK, TMEDA; δ) wet silica. R = H or alkyl.

Cyclopropanation of the key intermediates, the 6-(diethoxymethyl)-5-hydroxy-1-cyclohexenecarbaldehydes (e.g. **6**), followed by deprotection of the acetal functionality and elimination (as suggested in Figure 3), would yield the desired bicyclo[4.1.0]hept-2-ene-1,2-dicarbaldehydes (e.g. **14**).



6: R = H
7: R = CH_3
8: R = $(CH_2)_6CH_3$
9: R = H
10: R = CH_3
11: R = $(CH_2)_6CH_3$
12: R = H
13: R = CH_3
14: R = H
15: R = CH_3
16

Figure 3. α) DMSY; β) wet silica; χ) $NaHCO_3$ on silica. a: R'=H; b: R'=Ac; c: R'=TBDMS

α,β-Unsaturated ketones are known to undergo conjugate addition with dimethyl sulfoxonium methylide (DMSY),[10] giving the corresponding cyclopropyl ketone in moderate to good yields even when the double bond is tetrasubstituted.[11-13] However, to our knowledge no report of the cyclopropanation of unsaturated aldehydes by DMSY has appeared, although for acrolein and monosubstituted acrolein conjugate cyclopropanation with the more stable ethyl-(dimethylsulfuranylidene) acetate (EDSA), yielding the corresponding cyclopropyl aldehyde-ester has been reported.[14] In the present paper we show that cyclopropanation of tri- and tetrasubstituted unsaturated aldehydes with DMSY is feasible, and report the synthesis of two analogues of isovelleral (**3**) that may be useful in the study of the bioactivities of this sesquiterpene.

Two cyclopropanation procedures were found useful (see Table 1). Applying slightly modified Corey-Chaykovsky conditions[15] (procedure A), the unprotected enal alcohol **6a** as well as the acetate **6b** were cyclopropanated to compounds **9a** and **9b**, although the yields after purification were only modest. No 1,2-addition could be observed. However, these same conditions were not very useful for the cyclopropanation of derivatives having an alkyl group in the 2 position, no product being obtained from **7a** or **8a**, and only low yields of the acetate **10b** being obtained from **7b** when TMEDA was added to the reaction mixture. Neither raising the reaction temperature by 20 °C nor the addition of DMSO or salt[16] (KCl or KI) improved the yield. The TBDMS protected derivatives **6c** and **7c** gave no product at all.

DMSY can also be generated from trimethyl sulfoxonium iodide and *t*-BuOK in DMSO (procedure B), which was reported recently to efficiently transform aldehydes and ketones to epoxides.[17] Compared with the conventional reagents, it also has the advantage of being safer, as there have been reports of violent reactions between sodium hydride and DMSO.[18] It is also more suitable for small-scale reactions. Higher yields of the cyclopropane **10b** were obtained from the acetate **7b**, using this procedure, and there was no indication that 1,2-addition occurred in this case. Interestingly enough, procedure B worked less well with acetate **6b**. Only low yields of the cyclopropanated product were obtained, and these were accompanied by considerable amounts of the cyclopropane epoxide **16** (see Figure 3), obtained as a 50:50 diasteromeric mixture. The TBDMS derivative **7c** gave reasonable yields of the cyclopropanated product **10c**, and also the TBDMS protected heptyl derivative **8c** could be cyclopropanated, although it reacted slowly.

Table 1. Cyclopropanation of Cyclohexencarbaldehydes **6**, **7** and **8** to Form Compounds **9**, **10** and **11**.

Substrate	Procedure[a]	Equivalents[b]	Time[c]	Yield (%)[d]
6a	A	1.3	1	20
6b	A	1.4	0.5	24
7b	A	3	6	10
6b	B	3	15	7[e]
7b	B	3	20	65
7c	B	2	18	52
8c	B	2	84	29[f]

[a]Procedure A: 0.4 M DMSY in THF. Procedure B: Me_3SOI, *t*-BuOK in DMSO. See the Experimental section for details. [b]Equivalents of DMSY. [c]Reaction time in hours at 20 °C. [d]Isolated yields after chromatography. [e]The epoxide **16** was the major product. [f]50 % of the starting material remained.

It should be noted that although the yields stated in Table 1 are moderate, analyses of the crude reaction products by TLC, GC and ^1H NMR showed the cyclopropanation to normally proceed well.

The cyclopropanation reaction is completely steroselective, showing the same selectivity in both procedures. The stereochemistry of the cyclopropyl derivative **10b** was determined by a NOESY experiment, a strong correlation being observed between the acetal proton and one of the cyclopropane protons, whereas the other cyclopropane proton was correlated with the C-6 methyl protons. In the absence of overwhelming steric factors, the addition to the cyclohexenal (which predominantly exists in a diaxial conformation[9]) favours the formation of an axial carbon-carbon bond at the site of initial attack, and the preference for axial attack may be attributed to stereoelectronic control.[11] The addition from the same side as the acetal would generate a more stable half-chair cyclohexane enolate, while addition from the other side would generate a less stable boat conformation of the enolate.[11]

Although the acetal of compound **10c** was rapidly (minutes) hydrolysed with amberlyst 15[19] (the acetates **9b** and **10b** decomposed under the same conditions), the slower but milder wet silica conditions[20] were used for the hydrolysis of the acetals, producing the dialdehydes **12b**, **13b** and **13c** in quantitative

yields. Elimination of the acetates by the addition of sodium hydrogen carbonate directly to the silica suspension proceeded smoothly, the dialdehydes **14** and **15** being obtained in quantitative yields from the acetates **9b** and **10b**.

The mutagenicity of the two derivatives **14** and **15** towards the Ames' Salmonella tester strains TA98 and TA100 in the absence of metabolic activation (S9 mix) was compared with that of isovelleral (**3**) and merulidial (**5**), and the results are presented in Table 2.

Table 2. The Mutagenic Activity in the Salmonella/Microsome Assay[21] of Compounds **3**, **5**, **14** and **15** in the Absence of Metabolic Activation.

Compound (No.)	μg/plate[a]	Mutagenic response[b]		Mutagenic activity[c]	
		TA98	TA100	TA98	TA100
3	0.38	$66^{0.98}$	$79^{0.96}$	43	49
5	20	$67^{0.98}$	$77^{0.90}$	0.90	0.99
14	0.25	$159^{0.97}$	$784^{0.98}$	83	470
15	4	$198^{0.99}$	$385^{0.98}$	8.0	16

[a]The highest non-toxic dose. Each plate contains 20 ml of medium. [b]The mutagenic response is recorded as the number of revertant colonies in excess of the solvent control at the given concentration. Superscripts are correlation coefficients. [c]The mutagenic activity is given by the slope of the dose-response curve in number of excess revertants per nmole.

The mutagenic activities of isovelleral (**3**) and merulidial (**5**) are approximately the same as those determined in a previous investigation.[7] The mutagenic activity of the 6-methyl derivative **15** is lower compared to isovelleral (**3**), while the mutagenic activity of compound **14** is more than 10 times higher than that of compound **15**. This strongly supports the assumption that a nucleophilic attack on C-6 in compounds **14** and **15** (and on the corresponding carbon in the dialdehydes **3**, **4** and **5**) is important for the mutagenicity of these compounds.

EXPERIMENTAL

^{1}H NMR (300 and 500 MHz) and ^{13}C NMR (75 MHz) were recorded at room temperature using a Varian XL 300 (300 and 75 MHz) or a Bruker ARX 500 (500 MHz) spectrometer in $CDCl_3$ solutions. The chemical shifts are given in ppm, the solvent peaks (7.26 and 77.0 ppm, respectively) serving as reference, and the coupling constants J in Hz. Air and/or moisture sensitive reactions were carried out in oven-dried glassware under argon atmosphere using dry solvents. EI and CI (NH_3) mass spectra were recorded by a JEOL SX102 spectrometer at 70 eV. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel coated glass plates (Merck 60 F_{254}) using UV and/or p-anisaldehyde and

heat as the developing agents. Flash column chromatography was performed with Merck 60 silica gel (0.040-0.063 mm) using mixtures of heptane and ethyl acetate. GC analyses were performed with a Varian 3700 equipped with a J &W Scientific DB-5. 30m x 0.25 mm i.d. capillary column. The carrier gas was He (12 Psi), the injector temperature 250° C, and the detector temperature 270° C. Melting points, which are uncorrected, were determined using a Reichert microscope. Compounds **6a**, **6c**, **7a**, **7c**, **8a** and **8c** were prepared as described previously.[9] The Salmonella/microsome assay was made according to the standard procedure,[21] using plates containing a total of 20 ml of substrate. TA98 is a frameshift mutant strain and TA100 is a base-pair substitution mutant strain. All plates were triplicated, and at least 5 concentration levels (differentiated by a factor of 2) of each compound were tested. Acetone was used as the solvent throughout.

General procedure for the acetylation of the alcohols 6a and 7a.

Acetic anhydride (ca 100 equiv) was added to a stirred solution of the alcohol in pyridine containing catalytic amounts of DMAP. When the starting material had disappeared (according to TLC analysis), a saturated solution of $NaHCO_3$ was added and the mixture was extracted three times with diethyl ether. Washing with brine, drying with $MgSO_4$ and evaporation of the solvent gave the acetates in quantitative yield.

5-Acetoxy-6-(diethoxymethyl)-1-cyclohexenecarbaldehyde (6b).

Colourless oil. ^{1}H NMR δ (mult., *J*): 1.08 (t, *J*= 7.1, $CH_2C\underline{H}_3$), 1.22 (t, *J*=7.1, $CH_2C\underline{H}_3$), 1.85-2.00 (m, 4-H), 1.97 (s, Ac), 2.05-2.20 (m, 4-H), 2.34-2.43 (m, 3-H_2), 2.95-3.00 (m, 6-H), 3.25-3.37 (m, 1H, $C\underline{H}_2CH_3$), 3.53-3.75 (m, 3 H, $C\underline{H}_2CH_3$), 4.61 (d, *J*=4.1 Hz, $C\underline{H}(OEt)_2$), 5.50-5.55 (m, 5-H), 6.97 (m, 2-H), 9.43 (s, CHO). ^{13}C NMR δ: 15.0, 15.2, 21.3, 22.2, 23.6, 40.4, 63.6, 63.7, 67.0, 101.9, 137.8, 152.6, 170.2, 193.8. EIMS (*m/z*): 270.1429 (M^+, 5%, $C_{14}H_{22}O_5$ requires 270.1467), 220 16%), 165 (98%), 137 (53%), 135(72%), 103 (100%).

5-Acetoxy-6-(diethoxymethyl)-2-methyl-1-cyclohexenecarbaldehyde (7b).

White crystals mp 39-40 °C (diethyl ether). ^{1}H NMR δ (mult., *J*): 1.09 (t, *J*=7.0, $CH_2C\underline{H}_3$), 1.21 (t, *J*=7.0, $CH_2C\underline{H}_3$), 1.75-1.90 (m, 4-H), 1.97 (s, Ac), 2.10-2.40 (m, 4-H, 3-H_2), 2.20 (s, C-2 Me), 3.04-3.10 (m, 6-H), 3.25-3.38 (m, 1 H, $C\underline{H}_2CH_3$), 3.50-3.75 (m, 3 H, $C\underline{H}_2CH_3$), 4.50 (d, *J*=4.2, $C\underline{H}(OEt)_2$), 5.45-5.51 (m, 5-H), 10.10 (s, CHO). ^{13}C NMR δ: 15.1, 15.2, 18.8, 21.3, 23.4, 29.7, 40.5, 63.5, 63.5, 67.5, 102.5, 130.0, 157.3, 170.2, 191.1. EIMS (*m/z*): 284.1603 (M^+, 3%, $C_{15}H_{24}O_5$ requires 284.1624, 255 (8%), 239 (20%), 195 (53%), 179 (95%), 149 (58%), 103 (100%).

General procedure A for cyclopropanation.

The enal was added in one portion to a solution of dimethylsulfoxonium methylide (1.5 equiv) in THF. The resulting yellow solution was stirred at rt for 0.5-6h after which the reaction was quenched with saturated NH_4Cl. Extraction with diethyl ether followed by washing with saturated brine, drying with Na_2SO_4 and evaporation of the solvent gave the crude product, which was then purified by flash chromatography on silica gel.

3-Hydroxy-2-(diethoxymethyl)-bicyclo[4.1.0]heptane-1-carbaldehyde (9a).

Colourless oil. ^{1}H NMR δ (mult., *J*): 0.83-0.90 (m, 7-Ha), 1.19 (t, *J*=7.0, $CH_2C\underline{H}_3$), 1.25 (t, *J*=7.0, $CH_2C\underline{H}_3$), 1.39-1.51 (m, 7-Hb, 5-H_2), 1.60-1.70 (m, 4-H_2), 2.17-2.30 (m, 6-H), 2.67 (dd, *J*=5.9 and 8.5, 2-H), 3.45-3.66 (m, 3-H, $C\underline{H}_2CH_3$), 3.70-3.91 (m, $C\underline{H}_2CH_3$), 4.48 (d, *J*=5.9, $C\underline{H}(OEt)_2$), 9.09 (s, CHO). ^{13}C NMR δ: 15.2, 15.3, 18.9, 22.3, 22.6, 30.3, 34.2, 43.8, 64.4, 65.1, 67.7, 107.1, 202.0. CIMS (*m/z*): 260 (M + NH_4^+, 22%), 243 (M + H^+, 5%), 179 (100%); EIMS (*m/z*): 196 (6%), 179 (31%), 103 (100%), 75 (33%).

3-Acetoxy-2-(diethoxymethyl)-bicyclo[4.1.0]heptane-1-carbaldehyde (9b).

Colourless oil. ^{1}H NMR δ (mult., *J*): 1.15 (t, *J*=7.0, $CH_2C\underline{H}_3$), 1.17 (t, *J*=7.0, $CH_2C\underline{H}_3$), 1.27-1.36 (m, 7-H_2), 1.39-1.76 (m, 4-H_2, 5-H_2), 1.95-2.08 (m, 6-H), 2.02 (s, Ac), 3.07 (dd, *J*=2.3 and 5.6, 2-H), 3.41-3.57 (m, $C\underline{H}_2CH_3$), 3.63-3.75 (m, $C\underline{H}_2CH_3$), 4.32 (d, *J*=5.6, $C\underline{H}(OEt)_2$), 4.92-4.98 (m, 3-H), 8.84 (s, CHO). ^{13}C NMR δ: 14.6, 15.2, 15.2, 17.5, 20.6, 21.3, 23.0, 30.6, 38.0, 62.7, 63.9, 67.3, 104.0, 170.3, 201.7. CIMS (*m/z*): 302 (M + NH_4^+, 19%), 239 (31%), 179 (100%), 150 (43%); EIMS (*m/z*): 195 (12%), 149 (38%), 103 (100%), 75 (96%).

General procedure B for cyclopropanation.[17]

Trimethylsulfoxonium iodide[10] and DMSO were added to a dry flask . The mixture was stirred to give a clear solution, to which the enal was added. A solution of *t*-BuOK in DMSO was added to this, argon pressure being used, the resulting solution being stirred at rt for 9-24h under argon. The reaction was quenched by NH_4Cl solution and was extracted with diethyl ether, the ether extract being washed with brine and dried over $MgSO_4$. After filtration and evaporation of the solvent, the product was purified by flash chromatography on silica gel.

3-Acetoxy-2-(diethoxymethyl)-6-methyl-bicyclo[4.1.0]heptane-1-carbaldehyde (10b).

Colourless oil. ^{1}H NMR δ (mult., *J*): 1.14 (t, *J*=7.0, $CH_2C\underline{H}_3$), 1.17 (t, *J*=7.0, $CH_2C\underline{H}_3$), 1.26 (s, C-6 Me), 1.36 (d, *J*=5.2, 7-H), 1.39 (d, *J*=5.2, 7-H), 1.40-1.46 (m, 4-H), 1.65-1.75 (m, 4-H, 5-H), 1.76-1.83 (m, 5-H), 2.04 (s, Ac), 3.05 (br d, *J*=6.1, 2-H), 3.41-3.51 (m, $C\underline{H}_2CH_3$), 3.63-3.70 (m, $C\underline{H}_2CH_3$), 4.25 (d, *J*=6.1, $C\underline{H}(OEt)_2$), 4.99-5.01 (m, 3-H), 9.28 (s, CHO). ^{13}C NMR δ: 15.1, 15.2, 20.8, 21.0, 21.4, 23.1, 26.2, 28.6, 35.8, 39.5, 62.5, 64.1, 67.5, 103.9, 170.3, 202.2. EIMS (*m/z*): 298 (1%), 238.1581 (M^+ - HOAC, 3%, $C_{14}H_{22}O_3$ requires 238.1569), 209 (5%), 193 (9%), 165 (30%), 163 (43%), 103 (100%), 75 (76%).

3-[(tert-Butyldimethylsilyl)oxy]-6-methyl-2-(diethoxymethyl)-bicyclo[4.1.0]heptane-1-carbaldehyde (10c).

Colourless oil. ^{1}H NMR δ (mult., *J*): 0.04 and 0.08 (2 s, $Si(CH_3)_2$), 0.87 (bs, *t*-Bu and 7-H) 1.14 (t, *J*=7.0, $CH_2C\underline{H}_3$), 1.19 (t, *J*=7.0, $CH_2C\underline{H}_3$), 1.22 (s, C-6 Me), 1.20-1.28 (m, 4-H); 1.31 (d, *J*=4.9, 7-H), 1.41-1.52 (m, 4-H), 1.56 (ddd, *J*=3.0, 4.0 and 13.1, 5-H), 1.93-2.05 (m, 5-H), 2.90 (ddd, *J*=1.4, 3.0 and 6.7, 2-H), 3.38-3.54 (m, $C\underline{H}_2CH_3$), 3.58-3.77 (m, $C\underline{H}_2CH_3$), 3.98 (ddd, *J*=1.6, 3.1 and 4.7, 3-H), 4.07 (d, *J*=6.7, $C\underline{H}(OEt)_2$), 9.31 (s, CHO). ^{13}C NMR δ: -4.9, -4.6, 15.2, 15.2, 17.9, 20.3, 20.9, 25.4, 25.7 (*t*-Bu), 28.8, 36.1, 43.2, 62.7, 63.7, 64.2, 104.5, 202.9. EIMS (*m/z*): 370. 2556 (M^+, 2%, $C_{20}H_{38}O_4Si$ requires 370.2539), 313 (7%), 267 (84%), 223 (74%), 221 (70%), 193 (80%), 165 (65%), 147 (50%), 103 (100%) 75 (99%).

3-[(t-Butyldimethylsilyl)oxy]-6-(n-heptyl)-2-(diethoxymethyl)-bicyclo[4.1.0]heptane-1-carbaldehyde (11c).

Colourless oil. ^{1}H NMR δ (mult., *J*): 0.05 and 0.09 (2 s, $Si(CH_3)_2$), 0.78-0.92 (m, $(CH_2)_6C\underline{H}_3$), 0.88 (s, *t*-Bu), 1.10-1.35 (m, $(C\underline{H}_2)_6CH_3$, $-OCH_2C\underline{H}_3$, 4-H and 7-H), 1.15 (t, J=7.1, $CH_2C\underline{H}_3$), 1,34 (d, *J*=4.6, 7-H), 1.40-1.60 (m, 4-H and 5-H), 2.05-2.18 (m, 5-H), 2.89 (brd, *J*=6.4, 2-H), 3.37-3.55 (m, $C\underline{H}_2CH_3$), 3.59-3.78 (m, $C\underline{H}_2CH_3$), 3.94-3.99 (m, 3-H), 4.09 (d, *J*=6.4, $C\underline{H}(OEt)_2$), 9.31 (s, CHO). ^{13}C NMR δ: -4.9, -4.8, 14.1, 15.2, 15.2, 17.9, 20.6, 22.3, 22.7, 25.8 (*t*-Bu), 25.9, 27.5, 29.3, 29.8, 31.8, 33.7, 34.4, 35.8, 43.3, 62.9, 63.7, 64.3, 104.6, 202.6. EIMS (*m/z*): 454 (1%), 408 (10%), 397.2783 (M^+ - *t*-Bu, 6%, $C_{22}H_{41}O_4Si$ requires 397.2774), 351 (78%), 307 (45%), 305 (73%), 277 (71%), 249 (63%), 231 (44%), 103 (100%), 75 (98%).

3-Acetoxy-2-(diethoxymethyl)-1-(methyloxirane)-bicyclo[4.1.0]heptane (16).

Colourless oil, 1:1 mixture of 2 diastereomers. ^{1}H NMR δ (mult., *J*): 0.34-0.46 (m, 7-H), 0.58 (dd, *J*=5.0 and

9.4, 7-H), 0.95-1.1 (m, 6-H), 1.15-1.35 (m, $CH_2\underline{CH}_3$ and 4-H), 1.50-1.70 (m, 4-H, 5-H), 1.75-2.10 (m, 5-H), 2.02 and 2.05 (2 s, Ac), 2.18-2.30 (m, 2-H), 2.44 (dd, J =2.6 and 5.3, epoxide), 2.63-2.69 (m, epoxide), 3.01-3.05 (m, epoxide), 3.14-3.17 (m, epoxide), 3.40-3.50 (m, $\underline{CH}_2CH_3$), 3.50-3.70 (m, $\underline{CH}_2CH_3$), 4.29 (d, J =1.5, $\underline{CH}(OEt)_2$), 4.32 (d, J =2.5, $\underline{CH}(OEt)_2$), 4.90-4.96 (m, 3-H). ^{13}C NMR δ: 7.0, 9.3, 11.2, 13.8, 15.3, 15.4, 17.3, 17.5, 19.0, 19.6, 21.3, 21.4, 21.9, 22.2, 41.4, 46.0, 46.7, 55.8, 56.3, 61.0, 61.5, 63.5, 64.5, 67.9, 68.2, 103.9, 104.0, 170.3, 170.4. CIMS (*m/z*): 316 (M + NH_4^+, 14%), 299 (M + H^+, 8%), 193 (100%). EIMS (*m/z*): 298.1791 (M^+, 3%, $C_{16}H_{26}O_5$ requires 298.1780), 226 (5%), 207 (10 %), 193 (19%), 147 (32%), 119 (63%), 104 (100%), 91 (88%), 79 (61%).

General procedure for Acetal Hydrolysis. [20]

An aqueous solution of 10% oxalic acid (0.1 ml) was added to a suspension of silica gel (0.9 g) in 5 ml of CH_2Cl_2. After stirring of the mixture for 2-3 min, the acetal (0.1 g) was added and stirring was continued at rt for 30 h. The reaction was stopped by filtration, the silica gel being washed with additional EtOAc. Evaporation of the solvent gave the pure (according to ^1H NMR and TLC) dialdehydes as unstable oils.

3-Acetoxy-bicyclo[4.1.0]heptane-1,2-dicarbaldehyde (12b).

^1H NMR δ (mult., J): 0.90 (dd,J=5.9 and 13, 7-H), 1.28-1.40 (m, 4-H) 1.47 (dd,J=5.9 and 9.6, 7-H), 1.63-1.83 (m, 4-H, 5-H), 2.00-2.17 (m, 6-H), 2.03 (s, Ac), 3.83 (brd, J=3.4, 2-H), 5.22-5.28 (m, 3-H), 8.6 (bs, CHO), 9.5 (s, CHO). ^{13}C NMR δ: 14.9, 17.1, 18.1, 21.1, 22.7, 29.6, 46.4, 64.8, 170.1, 198.2, 199.0. CIMS (*m/z*): 228 (M + NH_4^+, 88%), 168 (100%). EIMS (*m/z*): 168 (8%), 150.0667 (M^+ - HOAC, 19%, $C_9H_{10}O_2$ requires 150.0681), 122 (100%), 107 (42%), 93 (64%), 91 (48%), 79 (61%), 77 (52%).

3-Acetoxy-6-methyl-bicyclo[4.1.0]heptane-1,2-dicarbaldehyde (13b).

^1H NMR δ (mult., J): 1.07 (d J=5.9, 7-H), 1.20-1.34 (m, 4-H), 1.47 (s, C-6 Me), 1.60 (d, J=5.9, 7-H), 1.70-1.90 (m, 4-H, 5-H_2), 2.05 (s, Ac), 3.88-3.91 (m, 2-H), 5.30-5.35 (m, 3-H), 9.21 (bs, CHO), 9.42 (s, CHO); ^{13}C NMR δ: 21.2, 22.0, 22.8, 23.0, 25.8, 27.5, 34.1, 46.9, 64.9, 142.7, 198.2, 200.2. EIMS (m/z): 224.1066 (M^+, 3%, $C_{12}H_{16}O_4$ requires 224.1048), 182 (92%), 164 (45%), 135 (53%), 121 (39%), 107 (47%), 91 (68%), 79 (60%), 43 (100%).

3-[(tert-Butyldimethylsilyl)oxy]-6-methyl-bicyclo[4.1.0] heptane-1,2-dicarbaldehyde (13c).

^1H NMR δ (mult., J): 0.05 and 0.07 (2 s, $Si\underline{(CH_3)_2}$), 0.86 (s, t-Bu), 0.98 (d, J=5.6, 7-H), 1.09-1.22 (m, 4-H), 1.42 (s, C-6 Me), 1.46-1.67 (m, 4-H, 5-H), 1.55 (d, J=5.6, 7-H), 2.01 (ddd, J=4.8, 4.8 and 12.9, 5-H), 3.70-3.74 (m, 2-H), 4.22-4.28 (m, 3-H), 9.21 (s, CHO), 9.44 (s, CHO). ^{13}C NMR δ: -5.1, -4.8, 17.9, 22.0, 23.0, 25.7, 26.0, 27.2, 34.3, 50.3, 62.5, 200.5, 200.7. EIMS (*m/z*): 296 (1%), 239.1121 (M^+ - t-Bu, 95%, $C_{12}H_{19}O_3Si$ requires 239.1103), 147 (57%), 129 (91%), 119 (57%), 91 (47%), 75 (100%), 73 (78%).

General procedure for elimination.

The acetal hydrolyses (see above) were quenched with solid $NaHCO_3$ (40 equiv) and stirred for another 2 h. Filtration and evaporation gave the pure (according to ^1H-NMR and TLC) unsaturated dialdehydes as weakly yellow oils in quantitative yields. Flash chromatography on silica gel gave the ene-dial in 60-70% yield from the corresponding acetal.

Bicyclo[4.1.0]hept-2-ene-1.2-dicarbaldehyde (14).

Colourless oil. ^1H NMR δ (mult., J): 1.00 (dd J=4.4 and 6.8, 7-H), 1.80-1.88 (m, 5-H), 1.92-2.20 (m, 4-H, 5-H and 7-H_2), 2.4-2.55 (m, 4-H), 6.87 (dd, J=3.3 and 5.8, 3-H), 9.56 (s, CHO), 9.78 (s, CHO); ^{13}C NMR δ: 19.2, 21.9, 22.2, 27.6, 29.2, 140.7, 149.4, 192.5, 199.5. EIMS (*m/z*): 150. 0685 (M^+, 72%, $C_9H_{10}O_2$ requires 150.0681), 122 (41%), 107 (66%), 103 (85%), 91 (86%), 79 (94%), 77 (100%).

6-Methyl-bicyclo[4.1.0]hept-2-ene-1.2-dicarbaldehyde (15).

White solid mp 60-70° C. ^{1}H NMR δ (mult., *J*): 1.04 (d, *J*=4.6, 7-H), 1.19 (s, C-6 Me), 1.72-1.83 (m, 5-H), 1.92 (d,*J*=4.6, 7-H), 2.00-2.26 (m, 4-H and 5-H), 2.43-2.56 (m, ,4-H), 6.86 (dd, *J*=2.8 and 6.2, 3-H), 9.50 (s, CHO), 9.69 (s, CHO); ^{13}C NMR δ: 19.6, 22.9, 24.3, 27.3, 32.6, 34.7, 142.0, 149.5, 192.4, 198.1. EIMS (*m/z*): 164.0844 (M+, 56%, $C_{10}H_{12}O_2$ requires 164.0837), 136 (50%), 121 (55%), 91 (100%), 79 (71%), 77 (64%).

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