117. Short Syntheses of (±)-Grandisol and (±)-Lineatin *via* a Common Intermediate

by **Ivana Aljancic-Solaja**[1]), **Max Rey**, and **André S. Dreiding***

Organisch-Chemisches Institut der Universität Zürich, Winterthurerstr. 190, CH-8057 Zürich

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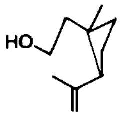
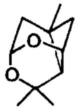
A 6-step synthesis of (±)-grandisol (**1**) is presented, which involves dichloroketene addition to 3-methyl-3-butenyl acetate (**4**), reductive dechlorination of the adduct **6** to the ketone **7** and saponification to **8**, aldolization of **7** or **8** with acetone and cyclization to the bicyclic ketone **9**, *Wolff-Kishner* reduction to **14**, and finally ring opening to **1**. Since **9** is a known intermediate of the synthesis of (±)-lineatin (**2**), the latter can now be obtained in 6 steps.

We present convenient and stereoselective syntheses of (±)-grandisol (**1**)[2]) and (±)-lineatin (**2**)[3]) involving 6 steps each from commercially available 3-methyl-3-butenol (**3**). The first 4 (new) steps lead to the common intermediate **9**, which has already been transformed [5] to **2** and is now converted to **1**.



1



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The acetate **4** (94% yield from **3**) was reacted with dichloroketene **5**, prepared *in situ* from trichloroacetyl chloride and Zn, to give the dichlorocyclobutanone **6** *(Scheme 1)*[4]). Dechlorination of **6** with Zn afforded the C_s-symmetrical acetoxy ketone **7** (63% from **4**), which was saponified to the hydroxy ketone **8** (85%).

Reaction of **7** or **8** with acetone in the presence of NaOH/H_2O and a phase-transfer catalyst ($Et_3(PhCH_2)N^+Cl^-$) introduced the remaining 3 C-atoms at one of the two enantiotopic CH_2 groups of the 4-membered ring to yield the bicyclic keto ether **9** (39% from **8** or 34% from **7**). This transformation involved an aldol condensation with dehydration (to **10**) and an intramolecular *Michael*-type addition of the OH group to the conjugated double bond. Obviously, the AcO group of **7** was hydrolyzed at some intermediate stage. The conditions for this aldol condensation (see *Exper. Part*) are essential for its success. As by-products, we also observed some of the hydroxy enone **10**, the keto

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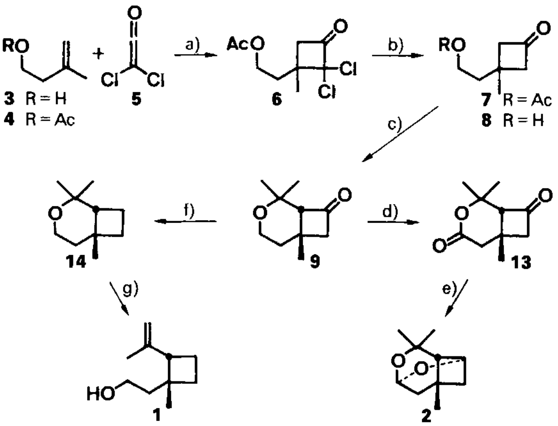
[1]) On leave of absence from Institute of Chemistry, Technology and Metallurgy, Belgrade, Jugoslavia.

[2]) Aggregation pheromone component isolated from *Anthonomus grandis* (Curculionidae, Coleoptera) [1]. There are 21 syntheses of grandisol (**1**) [2].

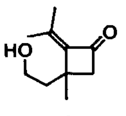
[3]) Aggregation pheromone component produced by *Trypodendron lineatis* (Scolytidae, Coleoptera) [3]. There are 10 syntheses of lineatin (**2**) [4–6].

[4]) A [2 + 2] addition of dichloroketene to construct the cyclobutane ring of **2** was also used in [5] and [6].

Scheme 1



a) Cl_3CCOCl, Zn, Et_2O. b) Zn, AcOH, pyridine. c) CH_3COCH_3, 30% aq. NaOH soln., $Et_3(PhCH_2)N^+Cl^-$. f) NH_2NH_2, K_2CO_3, triethylene glycol, 180–220°. d) RuO_4 [5]. g) $LiN(i\text{-}Pr)_2$, hexane. e) DIBAH, H_3O^+ [5].



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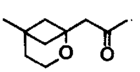

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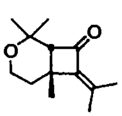

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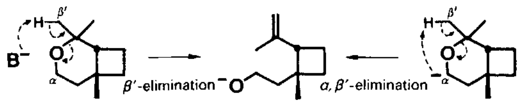
ether **11**, and the enone **12**. Keto ether **9** and hydroxy enone **10** were found to be interconvertible, a 72:28 equilibrium being reached from both sides under the aldol reaction conditions. Keto ether **11** resulted from an alternative aldol condensation, namely by attack of the enolate of acetone at the C=O group of **8**, followed by an intramolecular *Michael* addition of the OH group to the enone system. The success of our synthetic approach is due to the fact that the cyclization **10**→**9** causes the desired stereoselectivity by thermodynamic preference of the *cis*-fusion of the six-membered to the four-membered ring.

The bicyclic keto ether **9** had previously been prepared by another procedure and been converted to lineatin (**2**) by RuO_4 oxidation (→**13**) followed by double carbonyl reduction with diisobutylaluminium hydride (DIBAH) and acidic workup [5]. Thus, our synthesis of **9** represents a formal total synthesis of **2**.

Scheme 2



Our conversion of **9** to (±)-grandisol (**1**) starts with a *Wolff-Kishner* reduction to the bicyclic ether **14** (85%). Simple $LiN(i\text{-}Pr)_2$ treatment then gave **1** (95%). The ring opening **14**→**1** may have occurred by direct β'- and/or by indirect, intramolecular α,β'-elimination (*Scheme 2*). Such reactions are known [7] to occur with acyclic dialkyl ethers upon treatment with alkyl lithium or alkyl sodium.

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Experimental Part

1. *General.* Anal. GC: *SE-54 WCOT* column (25 × 0.3 mm), H_2 as carrier gas, FI detector, split injection. LC: *Merck LiChroprep Si 60* on silica gel (40–63 μ) at 2–6 bar. IR: *Perkin-Elmer 298.* ^{1}H-NMR and ^{13}C-NMR: *Varian XL-200* (200 MHz) and *Bruker AM-400* (400 MHz); the ^{13}C-one-bond multiplicities were obtained from DEPT pulse spectra. MS: *Varian MAT 711* or *1129* (CI = chemical ionisation). GC/MS/IR: *SE-54* (25 m × 0.3 mm) or *OV-1701* (12 m × 0.3 mm) *WCOT* column coupled with a *Digilab-FTS-15*-FT-IR spectrometer with *Digilab* GC/C interface and a *Hewlett-Packard 5970B* mass selective detector, He as carrier gas.

2. *3-Methyl-3-butenyl Acetate* (**4**). Procedure given in [8] modified as follows: A mixture of 3-methyl-3-butenol (**3**; 21.5 g, 250 mmol), pyridine (21.8 g, 275 mmol), and Ac_2O (28.1 g, 275 mmol) was left at r.t. for 18 h, poured into ice/H_2O, acidified to pH 4 with 1N HCl and extracted twice with Et_2O. The extract was washed with sat. $NaHCO_3$ soln. and brine and dried ($MgSO_4$). Distillation through a short *Vigreux* column afforded 30.1 g (94%) of **4**, b.p. 143–145°/760 Torr ([8]: 143–145°/760 Torr), as a colourless oil, 99% pure by GC. IR (film): 3090*w*, 2980*m*, 1748*s*, 1657*w*, 1370*m*, 1245*s*, 1050*s*, 900*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.81, 4.74 (2 split *s*, 2 H−C(4)); 4.18 (*t*, J = 7, 2 H−C(1)); 2.34 (*t*, J = 7, 2 H−C(2)); 2.05 (*s*, CH_3COO); 1.76 (*t*, J = 1, CH_3−C(3)). MS (70 eV): no $M^{+\cdot}$, 73 (2), 69 (3), 68 (35), 67 (20), 43 (100).

3. *2-(2,2-Dichloro-1-methyl-3-oxocyclobutyl)ethyl Acetate* (**6**). To a stirred suspension of **4** (38.5 g, 300 mmol) and commercial *(Merck & Co.)* Zn(Cu) couple (58.5 g, 895 mmol) in dry Et_2O (900 ml), a soln. of CCl_3COCl (70.9 g, 390 mmol) in dry Et_2O (210 ml) was added dropwise within 4 h at reflux. After stirring for an additional 6 h at reflux, the excess of metal was filtered off, and the filtrate was washed with H_2O, sat. $NaHCO_3$, soln., and brine and dried ($MgSO_4$). Evaporation left 72.3 g of crude **6** as a dark brown oil. A pure sample of **6** (1.86 g, 68%) was obtained as a colourless oil by bulb-to-bulb distillation at 105°/0.05 Torr of 2.50 g of crude **6** from another experiment performed in the same way on a 27-mmol scale (5.90 g of crude **6**). IR (film): 2970*m*, 2930*m*, 1812*s*, 1742*s*, 1365*m*, 1235*s*, 1135*m*, 1045*m*, 990*m*, 760*m*. ^{1}H-NMR (200 MHz; $CDCl_3$): 4.25 (*t*, J = 6.7, CH_2CH_2O); 3.32, 2.86 (*AB*, J = 16.9, 2 H−C(4')); 2.29, 2.12 (2 *dt*, J = 14.5, 6.7, CH_2CH_2O); 2.08 (*s*, CH_3COO); 1.40 (*s*, CH_3−C(1')). MS (70 eV): no $M^{+\cdot}$, 200 (1), 198 (3), 196 (4), 161 (4), 140 (4), 138 (26), 136 (42), 101 (8), 43 (100). Anal. calc. for $C_9H_{12}Cl_2O_3$ (239.10): C 45.21, H 5.06; found: C 44.99, H 5.01.

4. *2-(1-Methyl-3-oxocyclobutyl)ethyl Acetate* (**7**). Crude **6** (72.2 g; see *Exper. 3*) was added dropwise to a stirred suspension of Zn dust (105.3 g, 1.61 mol) in AcOH (330 ml) and pyridine (48 ml) during 45 min at 35–40°. After stirring for 2 h at 40° and 2 h at 70°, the mixture was cooled, diluted with Et_2O (1200 ml), and the precipitated Zn salts were filtered off. H_2O (150 ml) was added to the filtrate and the mixture neutralized with solid $NaHCO_3$. The precipitated NaOAc was filtered off, the filtrate washed with brine and dried ($MgSO_4$). Evaporation left 67.3 g of a pale yellow oil which, after distillation through a short *Vigreux* column, afforded 32.3 g of **7**, b.p. 127–130°/14 Torr, as a colourless oil (63% from **4**; 96% pure by GC). IR (film): 2960*m*, 2920*m*, 2875*w*, 1785*s*, 1740*s*, 1390*m*, 1370*s*, 1240*s*, 1145*m*, 1040*m*. ^{1}H-NMR (200 MHz; $CDCl_3$): 4.19 (*t*, J = 6.9, CH_2CH_2O); 3.0–2.6 (*m*, 2 H−C(2'), 2 H−C(4')); 2.05 (*s*, CH_3COO); 2.00 (*t*, J = 6.9, CH_2CH_2O); 1.35 (*s*, CH_3−C(1')). MS (70 eV): no $M^{+\cdot}$, 128 (13), 110 (4), 68 (77), 43 (100). Anal. calc. for $C_9H_{14}O_3$ (170.21): C 63.51, H 8.29; found: C 63.19, H 8.32.

5. *3-(2-Hydroxyethyl)-3-methylcyclobutan-1-one* (**8**). To a stirred soln. of **7** (2.55 g, 15 mmol) in MeOH (50 ml), $Ba(OH)_2$ (1.28 g, 7.5 mmol) was added in small portions during 10 min at 0°. After 30 min, the mixture was warmed to r.t., the MeOH evaporated, and the residue stirred with dry Et_2O (30 ml) for several min. The insoluble material was filtered off, washed with Et_2O (10 ml), and the combined filtrates were dried ($MgSO_4$). Evaporation and bulb-to-bulb distillation at 90–95°/0.1 Torr afforded 1.63 g (85%) of **8** as a colourless oil, 100% pure by GC. IR (film): 3430*s*, 2960*s*, 1780*s*, 1650*w*, 1380*m*, 1140*m*, 1060*m*, 1040*m*. ^{1}H-NMR (200 MHz; $CDCl_3$): 3.79 (*t*, J = 6.7, 2 H−C(2')); 3.1–2.7 (*m*, 2 H−C(2), 2 H−C(4)); 1.93 (*t*, J = 6.8, 2 H−C(1')); 1.62 (*s*, OH, exchangeable with D_2O); 1.35 (*s*, CH_3−C(3)). MS (70 eV): no $M^{+\cdot}$, 113 (1), 111 (1), 110 (1), 100 (36), 68 (76), 67 (68), 56 (100), 41 (88). Anal. calc. for $C_7H_{12}O_2$ (128.17): C 65.59, H 9.44; found: C 65.82, H 9.64.

6. *2,2,6-Trimethyl-3-oxabicyclo[4.2.0]octan-8-one* (**9**). 6.1. *From* **8**. To a stirred soln. of **8** (0.64 g, 5 mmol) in acetone (10 ml, 136 mmol), 30% aq. NaOH soln. (5 ml, 50 mmol) and triethylbenzylammonium chloride (0.25 ml of a 1M soln. in H_2O) were added dropwise separately and simultaneously over 10 min at r.t. After stirring for 42 h, the mixture was extracted with Et_2O (3 × 20 ml), the combined extracts dried ($MgSO_4$), and the solvent removed at 100 Torr. The crude product consisted, according to GC and GC/MS/IR, of a mixture of 4-methyl-3-penten-2-one,

4-hydroxy-4-methyl-2-pentanone, 3,5,5-trimethyl-2-cyclohexen-1-one, **8**, **11**, **9**, **10**, and **12** (order of GC elution) in the ratio 14:33:3:5:4:28:5:6. Using tridecane as internal standard in GC, the yield for **9** was determined to be 50%, and the yields of **10**, **11**, and **12** were 10, 7, and 9%, resp.; the starting material was still present to the extent of 14%. LC (hexane/Et_2O 8:2) afforded a major fraction from which, after bulb-to-bulb distillation at 85°/2 Torr, 0.33 g (39%) of **9** were obtained as a colourless oil, 99% pure by GC. Spectral data: as reported in [5].

6.2. *From* **7**. Acetate **7** (0.85 g, 5 mmol) was reacted and worked up as described in *6.1* (stirring for 21 h). The crude product was treated once more with the same amounts of acetone, NaOH, and $Et_3(PhCH_2)N^+Cl^-$ (stirring for 20 h) and worked up as in *6.1*. The crude product consisted, according to GC and GC/MS/IR, of a mixture of 4-methyl-3-penten-2-one, 4-hydroxy-4-methyl-2-pentanone, 3,5,5-trimethyl-2-cyclohexen-1-one, **8**, **11**, **9**, **10**, and **12** in the ratio of 14:33:2:8:4:25:4:4. Using tridecane as internal standard, the yields estimated for **8**, **11**, **9**, **10**, and **12** were 21, 7, 42, 9, and 5%, resp. LC (hexane/Et_2O 8:2) gave, aside from 4-methyl-3-penten-2-one, two fractions. Repeated LC (hexane/Et_2O 8:2) of the faster moving fraction yielded a small amount of pure **12** and, after bulb-to-bulb distillation at 85°/2 Torr, 0.29 g (34%) of **9**, 98% pure by GC. From the other fraction, after repeated LC (hexane/Et_2O 1:1), small amounts of pure **11** and **10** were obtained as colourless oils.

1-(5-Methyl-2-oxabicyclo[3.1.1]hept-1-yl)propan-2-one (**11**): IR ($CHCl_3$): 2960*s*, 2920*s*, 2860*m*, 2730*w*, 1710*s*, 1455*m*, 1425*m*, 1362*m*, 1312*m*, 1240*m*, 1208*m*, 1085*m*, 1055*s*. ^{1}H-NMR (200 MHz; $CDCl_3$): 4.03 (*t*, *J* = 6.7, 2H–C(3')); 2.58 (*s*, 2H–C(1)); 2.15 (*s*, 3H–C(3)); 2.05–1.93, 1.69–1.64 (2 *m*, 2H–C(6'), 2H–C(7')); 1.86 (*t*, *J* = 6.7, 2H–C(4')); 1.10 (*s*, CH_3–C(5')). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 207.2 (*s*, C(2)); 77.5 (*s*, C(1')); 60.6 (*t*, C(3')); 52.5 (*t*, C(1)); 43.8 (2 *t*, C(6'), C(7')); 37.2 (*t*, C(4')); 36.4 (*s*, C(5')); 31.5 (*q*, *C*H_3–C(5')); 26.6 (*q*, C(3)). MS (70 eV): 153 (4), 140 (97), 111 (11), 110 (10), 98 (20), 69 (68), 68 (39), 43 (100). CI-MS: 169. Anal. calc. for $C_{10}H_{16}O_2$ (168.24): C 71.39, H 9.59; found: C 71.42, H 9.68.

3-(2-Hydroxyethyl)-2-isopropylidene-3-methylcyclobutan-1-one (**10**): IR (film): 3440*m*, 2930*m*, 2870*m*, 1738*s*, 1665*s*, 1440*m*, 1370*m*, 1172*m*, 1078*m*, 1020*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.9–3.6 (*m*, 2H–C(2')); 2.9, 2.58 (*AB*, *J* = 17, 2H–C(4)); 2.08, 1.80 (2 *s*, $(CH_3)_2C{=}C(2)$); 2.1–1.8 (*m*, 2H–C(1')); 1.43 (*s*, CH_3–C(3)); 1.35 (*s*, OH, exchangeable with D_2O). MS (70 eV): 168 (2, $M^{+\cdot}$), 153 (7), 137 (9), 125 (26), 107 (14), 82 (64), 67 (100), 55 (37). Anal. calc. for $C_{10}H_{16}O_2$ (168.24): C 71.39, H 9.59; found: C 71.53, H 9.65.

7-Isopropylidene-2,2,6-trimethyl-3-oxabicyclo[4.2.0]octan-8-one (**12**): IR (film): 2930*m*, 2870*m*, 1740*s*, 1665*s*, 1440*m*, 1065*m*, 740*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.9–3.6 (*m*, 2H–C(4)); 2.52 (*s*, H–C(1)); 2.08, 1.80 (2 *s*, $(CH_3)_2C{=}C(7)$); 2.1–1.9 (*m*, 2H–C(5)); 1.53, 1.40 (2 *s*, $(CH_3)_2C(2)$); 1.25 (*s*, CH_3–C(6)). MS (70 eV): 208 (7, $M^{+\cdot}$), 193 (7), 153 (7), 111 (100), 107 (13), 43 (23). Anal. calc. for $C_{13}H_{20}O_2$ (208.30): C 74.96, H 9.67; found: C 74.81, H 9.85.

7. *Equilibration of* **9** *and* **10**. A sample of pure **9** and a sample of pure **10** (each 3 mg, 0.018 mmol) were stirred separately, each with 30% aq. NaOH soln. (0.1 ml, 1 mmol) and $Et_3(PhCH_2)N^+Cl^-$ (5 µl of a 1M soln. in H_2O). After 30 min, the mixtures were extracted with Et_2O. GC showed the soln. in both samples to contain **9** and **10** in the ratio of 72:28.

8. *2,2,6-Trimethyl-3-oxabicyclo[4.2.0]octan* (**14**). To a soln. of **9** (0.97 g, 5.8 mmol) in triethyleneglycol (13 ml), hydrazine hydrate (5.6 ml, 116 mmol) was added and the mixture heated at 90° for 1 h, *i.e.* until GC showed the absence of **9**. After cooling to r.t., anh. K_2CO_3 (2.75 g, 19.9 mmol) was added and the mixture heated in a bulb-to-bulb distillation apparatus to 180° for 30 min and then to 220° for 30 min, while the product was allowed to distill into the receiver bulb. The distillate was diluted with 80 ml H_2O, extracted with pentane (2 × 30 ml), and the extract was washed with 1% HCl soln. (20 ml), H_2O (2 × 30 ml), and brine (30 ml) and dried ($MgSO_4$). The solvent was distilled off over a short *Vigreux* column at atmospheric pressure, and the residue was purified by bulb-to-bulb distillation at 95°/45 Torr to give 0.76 g (85%) of **14** [9] as a colourless oil, 96% pure by GC. IR (film): 2980*s*, 2950*s*, 2870*s*, 1465*m*, 1378*m*, 1365*m*, 1220*m*, 1095*m*, 1078*s*, 812*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.6–3.4 (*m*, 2H–C(4)); 2.0–1.1 (*m*, H–C(1), 2H–C(5), 2H–C(7), 2H–C(8)); 1.09, 1.06 (2 *s*, $(CH_3)_2C(2)$); 0.94 (*s*, CH_3–C(6)). ^{13}C-NMR (50.3 MHz, $CDCl_3$): 70.7 (*s*, C(2)); 57.7 (*t*, C(4)); 47.7 (*d*, C(1)); 35.5 (*t*, C(6)); 34.0, 32.7 (2 *d*, C(5), C(7)); 28.0, 26.3, 24.8 (3 *q*, $(CH_3)_2C(2)$, *C*H_3–C(6)); 18.2 (*t*, C(8)). MS (70 eV): no $M^{+\cdot}$, 88 (4), 74 (6), 70 (9), 61 (14), 45 (24), 43 (100). Anal. calc. for $C_{10}H_{18}O$ (154.25): C 77.86, H 11.76; found: C 77.80, H 11.76.

9. *2-Isopropenyl-1-methylcyclobutaneethanol* (= *Grandisol*; **1**). To a soln. of $Li(i\text{-}Pr)_2N$, prepared by dropwise addition of 1.4M BuLi in hexane (6.9 ml, 9.7 mmol) to $(i\text{-}Pr)_2NH$ (1.4 ml, 10 mmol) at – 78° with stirring, was added **14** (135 mg, 0.88 mmol). The mixture was kept 1 h at – 70°, allowed to warm to r.t. and then heated at 75–80° (oil bath) for 36 h. The mixture was poured into cold sat. NH_4Cl, extracted with Et_2O (2 × 20 ml), washed with 1% HCl soln. (20 ml) and brine (2 × 20 ml) and dried ($MgSO_4$). After removing the solvent at atmospheric pressure, the residual yellow oil was bulb-to-bulb distilled at 120–130°/14 Torr to afford 128 mg (95%) of **1** as a colourless oil, 96% pure by GC. IR, ^{1}H-NMR, MS: as reported in [9].

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