Synthesis and Derivatization of Bis-nor Wieland–Miescher Ketone

Tõnis Kanger,*[a] Kristin Raudla,[a] Riina Aav,[a] Aleksander-Mati Müürisepp,[a] Tõnis Pehk,[b] Margus Lopp[a]

[a] Department of Chemistry, Faculty of Science, Tallinn University of Technology, Akadeemia tee 15, Tallinn 12618, Estonia
Fax +372(6)202828; E-mail: kanger@chemnet.ee

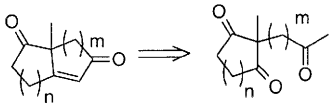
[b] National Institute of Chemical Physics and Biophysics, Akadeemia tee 23, Tallinn 12618, Estonia

Received 3 May 2005; revised 13 June 2005

Abstract: An efficient synthesis of bis-nor Wieland–Miescher ketone and its derivatives starting from commercially available 2-allyl-2-methylcyclopenta-1,3-dione is described.

Key words: alkylation, carbocycles, cyclization, epoxidation, Wittig reaction

Bicyclo[4.4.0]decanone and bicyclo[3.3.0]octanone skeletons are widely used in the construction of fused cyclohexanoid- and cyclopentanoid-containing natural products or their intermediates.[1] Wieland–Miescher ketone **1** is the most well-known representative of the former class of compounds. Its synthesis has been thoroughly investigated and described in a non-asymmetric[2] as well as in an asymmetric way.[3] The bis-nor derivative **2** of the above mentioned ketone is also a universal building block of the complex molecules, however, only little attention has been paid to its synthesis and functionalization. It is obvious that, in principle, the same synthetic route could be exploited to obtain both synthons (Scheme 1).

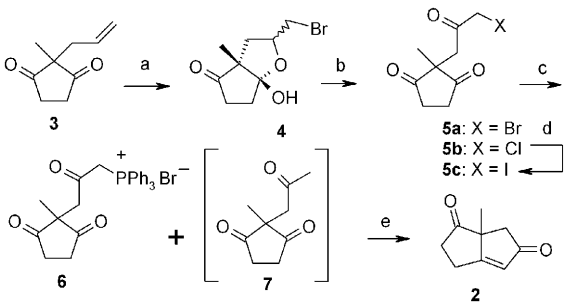


1: n = 2, m = 2
2: n = 1, m = 1

Scheme 1

Intramolecular aldol condensation of triketone is the most straightforward way to the targets. For Wieland–Miescher ketone this condensation approach is the main choice indeed. However, synthesis of the corresponding cyclopentane derivatives is a more difficult task because of their tendency to fragmentize under basic conditions.[4]

Previously, in order to obtain the title compound, different multistep procedures have been described. Among them, in the case of monoprotected cyclopentanedione, aldol condensation has been used. The intermediates for condensation were obtained via hydrolysis of nitroalkyl derivatives,[5] via hydration of alkynes using toxic $Hg(OAc)_2$[6] or by microbiological reduction.[7] Mori et al. synthesized compound **2** via the ring annulation of stannyl anion generated from allyl halide in the presence of CsF, followed by ozonolysis/dehydration or chlorination/oxidation procedure.[8] Trost et al. have used the intramolecular Wittig reaction for the cyclization.[9] The starting enol ether for it was obtained from the Pd-catalyzed reaction of 2-methylcyclopenta-1,3-dione with 3-acetoxy-2-ethoxyprop-1-ene. We report here a high-yield synthesis of bis-nor Wieland–Miescher ketone **2** starting, from commercially available 2-allyl-2-methylcyclopenta-1,3-dione **3** (Scheme 2).



Scheme 2 *Reagents and conditions*: (a) NBS, H_2O, acetone, 96%; (b) Jones reagent, acetone, 90%; (c) PPh_3, benzene; (d) NaI, acetone, quant (crude); (e) K_2CO_3, CH_2Cl_2, 40 °C, 76–79%

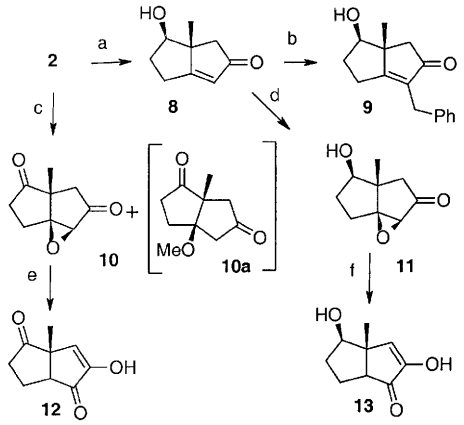
This functionalized cyclic dione **3** is an ideal precursor for ring annulation due to its symmetry features. Selective derivatization of the double bond in **3** was the first problem to solve. Instead of the desired epoxide, oxidation of compound **3** with MCPBA led to a Baeyer–Villiger reaction product, a δ-lactone.[10] However, bromohydroxylation of **3** with *N*-bromosuccinimide in acetone–water mixture afforded a bicyclic hemiacetal **4** as a ~1:1 mixture of diastereoisomers in nearly quantitative yield (96%). Lack of stereoselectivity in this step was overcome by converting compound **4** with Jones reagent to the corresponding α-halo ketone **5**. The bromine atom in the α-position to the carbonyl group could very easily be substituted with chloride. During the work-up procedure (washing the product with brine) halogen exchange took place and a mixture of bromo ketone **5a** and chloro ketone **5b** was obtained. When brine was not used in the work-up, bromo ketone **5a** was obtained as a single product in 90% yield. If instead of Jones reagent PCC was used, again a ~1:1 mixture of halo ketones **5a** and **5b** was obtained.

The final cyclization affording bis-nor Wieland–Miescher ketone with Wittig reagent[9] was studied in more detail. Two competitive reactions take place during the treatment

SYNTHESIS 2005, No. 18, pp 3147–3151
Advanced online publication: 16.09.2005
DOI: 10.1055/s-2005-916025; Art ID: Z08905SS

of bromo ketone **5a** with Ph_3P in refluxing benzene: formation of phosphonium salt **6** and reduction of bromide **5a** affording triketone **7** (in 12–34% yield). This by-product can be separated from the target compound by chromatography. It is known that reduction of α-bromo ketones to ketones by Ph_3P in nonpolar solvents is catalyzed by alcohols.[11] The same reaction takes place also in moist benzene.[12] To avoid the formation of triketone **7**, the reaction was carried out in carefully dried benzene (distilled from Na) and so the amount of triketone was reduced to 12%.[13] Generation of ylide from phosphonium salt was accomplished by the treatment of **6** with aqueous K_2CO_3. Subsequent cyclization in refluxing dichloromethane afforded bis-nor Wieland–Miescher ketone **2** in 79% yield (starting from **5a**). Alternatively, the mixture of bromide **5a** and chloride **5b** was converted to iodo ketone **5c** in acetone with NaI, followed by intramolecular Wittig reaction. This procedure resulted also in the target bicyclic compound **2**, but in a considerably lower yield (50%).

We have recently demonstrated that 1,2-diketones are valuable substrates for asymmetric oxidations affording nonracemic 3-hydroxy dicarbonyl compounds,[14] lactone acids[15] or spirodilactones[16] in high enantiomeric purity. In connection with our ongoing project on the use of the asymmetric oxidation in natural product synthesis[17] and to widen the synthetic scope of it, bis-nor Wieland–Miescher ketone **2** was transformed into new 1,2-diketone derivatives **12** and **13** (Scheme 3). These compounds are good starting materials for the asymmetric oxidation giving rise to bicyclic γ-lactones known as natural products with promising biological profile.[18]



Scheme 3 *Reagents and conditions*: (a) $NaBH_4$, $MeOH/CH_2Cl_2$, 94%; (b) NaH, BnBr, THF, 40%; (c) 0.1 M NaOH, H_2O_2, THF, 58%; (d) 5 M NaOH, H_2O_2, MeOH, 80%; (e) $BF_3{\cdot}OEt_2$, benzene, 64%; (f) 0.01 M H_2SO_4, 45%

Two easily distinguished carbonyl functionalities in bis-nor Wieland–Miescher ketone **2** allow the further derivatization. Analogous to the six-membered ring Wieland–Miescher ketone **1**, the reduction of the isolated carbonyl group in **2** is completely stereoselective affording only *cis*-substituted bicycle **8** in a 94% yield. It is important to avoid excess of $NaBH_4$ because of the reduction of enone moiety. The stereochemistry of the obtained hydroxyl group was established by NMR from the comparison of angular methyl carbon chemical shifts in **8** (18.42 ppm) and in model 3a-methyl-1,2,3,3a,4,5-hexahydropentalene (22.5 ppm).[19] More than 4 ppm high field shift of methyl carbon in **8** points to it *cis*-orientation with the vicinal OH group. The angular methyl group is most probably responsible for the high selectivity.

It has been shown earlier that it is possible to alkylate bis-nor Wieland–Miescher ketone **2** at the α-position of an isolated carbonyl group.[9a] However, we found that instead primary deprotonation of the hydroxyl group in **8** with NaH, enolization of enone takes place. Quenching the obtained dienolate with benzyl bromide affords the α-substituted product (enone **9**, in 40% yield) instead of the expected ether. Sterical hindrance in the surroundings of the angular methyl group must be again a significant directive factor that causes the unusual pathway. This finding gives us an access to the compounds that are alkylated in either ring of the bis-nor Wieland–Miescher ketone **2**.

Enones **2** and **8** were epoxidized with H_2O_2 under basic conditions. An investigation of the conditions that give rise to heightened levels of epoxides showed that bis-nor Wieland–Miescher ketone **2** is more sensitive to basic conditions and nucleophilic reagents than its derivative **8** (Table 1).

Table 1 Epoxidation of Enones **2** and **8**

No	Enone	Conditions	Product (Yield%)
1	**2**	5 M NaOH, MeOH, H_2O_2 (3 equiv), r.t., 1 h	mixture of compounds
2	**2**	0.1 M NaOH, MeOH, H_2O_2 (3 equiv), 0 °C, 3 h	**10** + **10a** (in 3.5:1 ratio)
3	**2**	0.1 M NaOH, THF, H_2O_2 (2 equiv), 0 °C, 2 h	**10** (58)
4	**8**	5 M NaOH, MeOH, H_2O_2 (3 equiv), r.t., 1 h	**11** (80)
5	**8**	0.1 M NaOH, MeOH, H_2O_2 (3 equiv), r.t., 20 h	**11** (52)

When MeOH was used as a solvent for epoxidation, the Michael addition of the methoxy group to enone **2** took place together with epoxidation (entry 2). Only the reaction in THF afforded the target in 58% yield (entry 3). At the same time, compound **8** was epoxidized in MeOH in 80% yield (entry 4). Strength of the base was also important for the epoxidation reaction: a stronger base caused the decomposition of enone **2** while it was obligatory for enone **8** (entries 1,4,5). Formation of epoxides **10** and **11** from **2** and **8** correspondingly was stereospecific: only *exo* products were formed, because *endo* products belong to the highly strained *trans*-bicyclo[3.3.0]octane derivatives. It is known that epoxidation of the conformationally more

flexible Wieland–Miescher ketone **1** leads to a mixture of *exo*- and *endo*-epoxides.[20]

Epoxides **10** and **11** were converted into the corresponding 1,2-diketones **12** and **13**. Differences in the properties of keto and hydroxy bis-nor Wieland–Miescher ketone derivatives were also observed in the acid-catalyzed rearrangement step – different reaction conditions were found necessary to rearrange keto epoxide **10** and hydroxy epoxide **11**. The former was rearranged with boron trifluoride in 58% yield while the latter epoxide was rearranged by refluxing in dilute sulfuric acid (0.01 M) in 45% yield (use of boron trifluoride led to decomposition of the starting epoxide).

In summary, we have shown an efficient synthetic sequence to a valuable intermediate – bis-nor Wieland–Miescher ketone **2**. Its derivatization was carried out via selective alkylation of the enone fragment or conversion into 1,2-diketones via epoxides. The application of these new intermediates in natural product synthesis is currently under study.

Full assignment of ^{1}H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra on a Bruker AMX500 instrument. Solvent peaks ($CHCl_3$, δ = 7.27, DMSO-d_5, δ = 2.50, $CDCl_3$, δ = 77.00, DMSO-d_6, δ = 39.50) were used as chemical shift references. The mass spectra were recorded on a Hitachi M80B spectrometer or on Hewlett-Packard GC-MS system (HP 5988A) using electron ionization (EI) at 70 eV. IR spectra were recorded on Perkin-Elmer Spectrum BX FTIR spectrometer. Elemental analyses were performed on a Perkin-Elmer C,H,N,S-Analyzer 2400. Reactions sensitive to oxygen or moisture were conducted under argon atmosphere in flame-dried glassware. Commercial reagents were generally used as received. Petroleum ether used had bp 40–60 °C.

2-Bromomethyl-6a-hydroxy-3a-methylhexahydro-4*H*-cyclopenta[*b*]furan-4-one (4)

To a solution of diketone **3** (1.1 g, 7.23 mmol) in acetone–H_2O (1:1.5, 90 mL), was added NBS (1.54 g, 8.67 mmol) at r.t. and the mixture was stirred for 3 h. After addition of H_2O (100 mL), acetone was evaporated and the residue was extracted with EtOAc (7 × 50 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by column chromatography (20% EtOAc in petroleum ether) affording a yellow oil, as ca. 3:2 mixture of 2-*endo* and 2-*exo* isomers, which solidified in the freezer; yield: 1.73 g (96%).

IR (film): 3419, 2966, 1744, 1153, 1062, 656 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ (*endo*-isomer) = 4.14 (m, 1 H, H-2), 3.50 and 3.49 (m, 2 H, CH_2Br), 2.53 (m, 1 H, H-3), 1.83 (dd, 1 H, *J* = 8.7, 13.1 Hz, H-3), 2.48 and 2.43 (m, 2 H, H-5), 2.12 and 2.38 (m, 2 H, H-6), 1.11 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 219.11 (C-4), 111.73 (C-6a), 77.56 (C-2), 59.25 (C-3a), 38.80 (C-3), 37.02 (CH_2Br), 35.72 (C-5), 30.44 (C-6), 15.74 (CH_3).

^{1}H NMR ($CDCl_3$): δ (*exo*-isomer) = 4.47 (m, 1 H, H-2), 3.31 (dd, 1 H, *J* = 5.2, 10.6 Hz, CH_2Br), 3.28 (dd, 1 H, *J* = 5.8, 10.6 Hz, CH_2Br), 2.52 (m, 2 H, H-5), 2.42 and 2.06 (m, 2 H, H-6), 2.27 (dd, 1 H, *J* = 5.8, 13.5 Hz, H-3), 2.06 (m, 1 H, H-3), 1.12 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 219.29 (C-4), 112.25 (C-6a), 76.69 (C-2), 58.64 (C-3a), 39.86 (C-3), 36.11 (C-5), 34.78 (CH_2Br), 30.30 (C-6), 16.23 (CH_3).

MS (EI): *m*/*z* (%) = 250, 248 (M$^+$, 10), 202 (7), 169 (5), 151 (21), 125 (29), 69 (42), 55 (68), 41 (100).

Anal. Calcd for $C_9H_{13}BrO_3$ (249.10): C, 43.40; H, 5.26. Found: C, 43.49; H, 5.14.

2-(3-Bromo-2-oxopropyl)-2-methylcyclopentane-1,3-dione (5a)

To a solution of hemiacetal **4** (1.24 g, 4.99 mmol) in acetone (20 mL), was added Jones reagent (2.8 mL, 7.49 mmol) at 0 °C and the mixture was stirred at r.t. for 24 h. *i*-PrOH (5 mL) was added and the mixture was stirred for 30 min at r.t. Then the mixture was poured into sat. aq solution of Na_2SO_4 (20 mL) and extracted with EtOAc (5 × 15 mL). The combined organic phases were dried ($MgSO_4$) and solvent was evaporated. The residue was purified by crystallization from EtOAc (5 mL) to afford white crystals; yield: 1.11 g (90%).

IR (KBr): 2996, 1716, 1390, 1080, 630 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.85 (s, 2 H, CH_2Br), 3.33 (s, 2 H, CH_2CO), 2.92 and 2.87 (m, 4 H, H-4,5), 1.09 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 215.51 (C-1,3), 200.31 (*C*OCH_2Br), 52.59 (C-2), 47.35 (*C*H_2CO), 34.63 (C-4,5), 32.42 (CH_2Br), 19.59 (CH_3).

MS (EI): *m*/*z* (%) = 248, 246 (M$^+$, 2), 204 (0.5), 167 (2.5), 151 (2), 125 (90), 69 (70), 41 (100).

Anal. Calcd for $C_9H_{11}BrO_3$ (247.09): C, 43.75; H, 4.49. Found: C, 43.88; H, 4.27.

6a-Methyl-2,3,6,6a-tetrahydropentalene-1,5-dione (2)

To a solution of bromo ketone **5a** (4.03 g, 16.30 mmol) in benzene (80 mL), was added PPh_3 (8.55 g, 32.60 mmol) under argon. After refluxing for 3 h, the mixture was cooled, diluted with CH_2Cl_2 (40 mL), and aq sat. solution of K_2CO_3 (50 mL) was added. The mixture was stirred for 30 min, then extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried ($MgSO_4$). After filtration, benzene was evaporated and the residue was stirred at 40 °C for 24 h in CH_2Cl_2 (100 mL). After evaporation of the solvent, the residue was purified by column chromatography (20–40% EtOAc in petroleum ether) affording bis-nor Wieland–Miescher ketone **2** as an oil; yield: 1.87 g (76%).

IR (film): 2970, 2928, 1752, 1709, 1635 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 5.94 (d, 1 H, *J* = 2.0 Hz, H-4), 3.09 and 3.02 (m, 2 H, H-3), 2.95 (ddd, 1 H, *J* = 2.6, 11.1, 19.1 Hz, H-2), 2.56 (d, 1 H, *J* = 18.0 Hz, H-6), 2.43 (td, 1 H, *J* = 8.9, 8.9, 19.1 Hz, H-2), 2.29 (d, 1 H, *J* = 18.0 Hz, H-6), 1.33 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 212.41 (C-1), 207.49 (C-5), 184.70 (C-3a), 126.02 (C-4), 56.67 (C-6a), 44.58 (C-6), 38.18 (C-2), 24.32 (C-3), 23.11 (CH_3).

MS (EI): *m*/*z* (%) = 150 (M$^+$, 20), 122 (53), 107 (24), 79 (100), 66 (17), 51 (30).

Anal. Calcd for $C_9H_{10}O_2$ (150.17): C, 71.98; H, 6.71. Found: C, 71.87; H, 6.77.

(6*R,6a*R**)-6-Hydroxy-6a-methyl-4,5,6,6a-tetrahydropentalen-2(1*H*)-one (8)**

A solution of ketone **2** (540 mg, 3.60 mmol) in a mixture of MeOH–CH_2Cl_2 (1:1, 72 mL) was cooled to 0 °C in an ice-bath and $NaBH_4$ (34 mg, 0.90 mmol) was added. After stirring for 15 min, acetone (5 mL) was added and the mixture was allowed to warm to r.t., following the addition of H_2O (1 mL) and drying ($MgSO_4$). Solvents were evaporated and the residue was purified by column chromatography (20–30% acetone in petroleum ether) affording a yellow oil; yield: 513 mg (94%).

IR (film): 3405, 2968, 1704, 1627, 1410, 1230, 1086 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 5.77 (dd, 1 H, *J* = 1.0, 2.2 Hz, H-3), 3.89 (dd, 1 H, *J* = 8.1, 9.5 Hz, H-6), 3.29 (br s, 1 H, OH), 2.78 and 2.53 (m, 2 H, H-4), 2.32 and 2.26 (each d, 2 H, *J* = 17.8 Hz, H-1), 2.23 and 2.03 (m, 2 H, H-5), 1.13 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 210.69 (C-2), 192.32 (C-3a), 125.24 (C-3), 77.57 (C-6), 53.23 (C-6a), 49.57 (C-1), 31.85 (C-5), 23.99 (C-4), 18.42 (CH_3).

MS (EI): *m*/*z* (%) = 152 (M^+, 12), 124 (63), 109 (100), 79 (71).

Anal. Calcd for $C_9H_{12}O_2$ (152.19): C, 71.03; H, 7.95. Found: C, 70.38; H, 8.06.

(6*R,6a*R**)-3-Benzyl-6-hydroxy-6a-methyl-4,5,6,6a-tetrahydropentalen-2(1*H*)-one (9)**

A suspension of NaH (9.2 mg, 0.23 mmol) in THF (3 mL) was cooled in an ice-bath under argon. A solution of enone **8** (105 mg, 0.69 mmol) in THF (4 mL) was added dropwise and the mixture was stirred for 30 min. A second portion of NaH (9.2 mg, 0.23 mmol) was added and after another 30 min, a third portion of NaH (9.2 mg, 0.23 mmol) was added. The mixture was stirred for additional 30 min followed by addition of benzyl bromide (0.16 mL, 1.38 mmol). The mixture was stirred for 4 h at 0 °C and for overnight at r.t. After addition of H_2O (20 mL), the mixture was extracted with EtOAc (4 × 20 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by column chromatography (10% EtOAc in petroleum ether) affording a yellow oil; yield: 67 mg (40%).

IR (film): 3411, 3028, 2966, 1698, 1652, 1603, 1495, 1083, 1041, 705 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.28 (t, 2 H, *J* = 7.4 Hz, *meta*-H_{arom}), 7.21 (t, 1 H, *J* = 7.4 Hz, *para*-H_{arom}), 7.18 (d, 2 H, *J* = 7.4 Hz, *ortho*-H_{arom}), 3.89 (dd, 1 H, *J* = 8.1, 9.5 Hz, H-6), 3.56 (d, 1 H, *J* = 15.3 Hz, PhCH_2), 3.43 (dd, 1 H, *J* = 1.1, 15.3 Hz, PhCH_2), 2.54 (m, 1 H, H-4), 2.37 and 2.34 (d each, 2 H, *J* = 17.7 Hz, H-1), 2.35 (br s, 1 H, OH), 2.33 (m, 1 H, H-4), 2.22 and 2.00 (m each, 2H, H-5), 1.15 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 209.11 (C-2), 184.62 (C-3a), 138.81 (C_{arom}), 135.83 (C-3), 128.55 (*o*-CH_{arom}), 128.41 (*m*-CH_{arom}), 126.11 (*p*-CH_{arom}), 78.10 (C-6), 51.14 (C-6a), 48.99 (C-1), 32.11 (C-5), 29.63 (PhCH_2), 22.93 (C-4), 18.66 (CH_3).

MS (EI): *m*/*z* = 242 (M^+), 214, 196, 181, 91, 77.

Anal. Calcd for $C_{16}H_{18}O_2$ (242.31): C, 79.31; H, 7.49. Found: C, 78.81; H, 7.55.

(1a*S,3a*R**,6a*S**)-3a-Methyltetrahydro-1a*H*-pentaleno[1,6a-*b*]oxirene-2,4-dione (10)**

To a solution of enone **2** (1.46 g, 9.74 mmol) in THF (50 mL), was added a solution of H_2O_2 (33% in H_2O, 1.77 mL, 19.47 mmol) at 0 °C, followed by dropwise addition of 0.1 M NaOH (48.70 mL, 4.87 mmol). After stirring for 2 h, the mixture was poured into a solution of brine (100 mL) and extracted with EtOAc (5 × 50 mL). The combined organic phase were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (10% acetone in petroleum ether), affording the target compound as white crystals; yield: 938 mg (58%).

IR (KBr): 3066, 2944, 2924, 1753, 1735, 1125, 1057, 1002 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.34 (s, 1 H, H-1), 2.88 (ddd, 1 H, *J* = 1.9, 10.5, 19.4 Hz, H-5), 2.69 (ddd, 1 H, *J* = 9.6, 10.5, 13.6 Hz, H-6), 2.67 (d, 1 H, *J* = 19.7 Hz, H-3), 2.52 (ddd, 1 H, *J* = 9.5, 9.6, 19.4 Hz, H-5), 2.17 (ddd, 1 H, *J* = 1.9, 9.5, 13.6 Hz, H-6), 2.10 (d, 1 H, *J* = 19.7 Hz, H-3), 1.25 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 213.91 (C-4), 206.36 (C-2), 75.41 (C-6a), 61.84 (C-1), 48.74 (C-3a), 42.69 (C-3), 36.72 (C-5), 21.04 (C-6), 16.85 (CH_3).

MS (EI): *m*/*z* = 166 (M^+), 138, 109, 95, 67.

Anal. Calcd for $C_9H_{10}O_3$ (166.17): C, 65.05; H, 6.07. Found: C, 64.99; H, 6.16.

(1a*S,3a*S**,4*R*,6a*S**)-4-Hydroxy-3a-methyltetrahydro-1a*H*-pentaleno[1,6a-*b*]oxiren-2(3*H*)-one (11)**

To a solution of enone **8** (108 mg, 0.71 mmol) in MeOH (7 mL), was added 33% H_2O_2 (0.19 mL, 2.13 mmol) at r.t., followed by dropwise addition of aq 5 M NaOH (0.035 mL, 0.18 mmol). After stirring for 1 h, the mixture was poured into brine (10 mL) and extracted with EtOAc (5 × 10 mL). The combined organic phases were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (10% acetone in petroleum ether), to afford a yellow oil; yield: 95 mg (80%).

IR (film): 3419, 2970, 1743, 1248, 1097, 1070, 1048, 883 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.88 (t, 1 H, *J* = 8.5 Hz, H-4), 3.21 (s, 1 H, H-1), 2.37 (d, 1 H, *J* = 19.0 Hz, H-3), 2.33 (m, 1 H, H-6), 2.27 (m, 1 H, H-5), 2.18 (br s, 1 H, OH), 2.04 (d, 1 H, *J* = 19.0 Hz, H-3), 1.88 (m, 2 H, H-5,6), 1.13 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 209.47 (C-2), 75.98 (C-4), 75.80 (C-6a), 62.77 (C-1), 44.98 (C-3a), 44.84 (C-3), 29.65 (C-5), 20.93 (C-6), 13.28 (CH_3).

MS (EI): *m*/*z* = 168 (M^+), 139, 124, 95, 69.

(3a*R,6a*R**)-5-Hydroxy-6a-methyl-2,3,3a,6a-tetrahydropentalene-1,4-dione (12)**

To a solution of epoxide **10** (53 mg, 0.32 mmol) in benzene (5 mL), was added $BF_3{\cdot}OEt_2$ (40 μL, 0.32 mmol). The resulting mixture was refluxed for 2 h. After addition of aq sat. $NaHCO_3$ solution (10 mL), the mixture was extracted with EtOAc (6 × 5 mL), and the combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (20% acetone in petroleum ether) to give **12**; yield: 34 mg (64%).

IR (KBr): 3151, 2974, 2932, 1739, 1690, 1608 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 6.32 (s, 1 H, H-6), 2.73 (m, 1 H, H-3a), 2.43 and 2.25 (m, 2 H, H-2), 2.14 and 2.15 (m, 2 H, H-3), 1.13 (s, 3 H, CH_3).

^{1}H NMR (DMSO-d_6): δ = 9.99 (s, 1 H, OH), 6.13 (s, 1 H, H-6), 2.68 (d, 1 H, *J* = 8.7 Hz, H-3a), 2.41 and 1.90 (m, 2 H, H-2), 2.11 and 2.10 (m, 2 H, H-3), 1.23 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 215.67 (C-1), 205.41 (C-4), 153.21 (C-5), 132.32 (C-6), 52.49 (C-3a), 51.76 (C-6a), 35.20 (C-2), 20.15 (C-3), 19.62 (CH_3).

^{13}C NMR (DMSO-d_6): δ = 216.49 (C-1), 204.89 (C-4), 154.56 (C-5), 131.40 (C-6), 52.21 (C-3a), 50.84 (C-6a), 34.90 (C-2), 19.78 (C-3), 19.66 (CH_3).

MS (EI): *m*/*z* = 166 (M^+), 138, 120, 110, 95.

Anal. Calcd for $C_9H_{10}O_3$ (166.17): C, 65.05; H, 6.07. Found: C, 65.01; H, 6.10.

(3a*R,4*R**,6a*R**)-2,4-Dihydroxy-3a-methyl-4,5,6,6a-tetrahydropentalen-1(3a*H*)-one (13)**

A mixture of epoxide **11** (40 mg, 0.24 mmol) and 0.01 M H_2SO_4 (5.5 mL) was heated at 100 °C for 24 h. The mixture was cooled and extracted with EtOAc (4 × 5 ml). The EtOAc extract was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (25% acetone in petroleum ether), affording a yellow solid; yield: 18 mg (45%).

IR (KBr): 3417, 3108, 2963, 2932, 1695, 1649, 1422, 1220, 1103, 966 cm^{-1}.

^{1}H NMR ($CDCl_3$ + CD_3OD): δ = 6.29 (s, 1 H, H-3), 3.87 (m, 1 H, H-4), 2.38 (d, 1 H, *J* = 10.1 Hz, H-6a), 2.22 and 1.67 (m, 2 H, H-6), 1.64 (m, 2 H, H-5), 1.26 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$ + CD_3OD): δ = 207.68 (C-1), 152.35 (C-2), 137.50 (C-3), 76.34 (C-4), 54.74 (C-6a), 51.43 (C-3a), 32.73 (C-5), 26.43 (C-6), 19.73 (CH_3).

MS (EI): *m*/*z* = 168 (M^+), 150, 122, 97, 79.

Acknowledgment

The authors thank Estonian Science Foundation for financial support (grant numbers 4976, 5628 and 5133) and Mrs Tiiu Kailas for IR and elemental analyses.

References

(1) (a) Shah, N.; Scanlan, T. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5199. (b) Kende, A. S.; Deng, W.-P.; Zhong, M.; Guo, X.-C. *Org. Lett.* **2003**, *5*, 1785. (c) Aav, R.; Kanger, T.; Pehk, T.; Lopp, M. *Synlett* **2000**, 529. (d) Inomata, K.; Barrague, M.; Paquette, L. A. *J. Org. Chem.* **2005**, *70*, 533. (e) Mulzer, J.; Kaselow, U.; Graske, K.-D.; Kühne, H.; Sieg, A.; Martin, H. J. *Tetrahedron* **2004**, *60*, 9599. (f) Subburaj, K.; Okamoto, S.; Sato, F. *J. Org. Chem.* **2002**, *67*, 1024. (g) Mukai, C.; Kobayashi, M.; Kim, I. J.; Hanaoka, M. *Tetrahedron* **2002**, *58*, 5225.

(2) Ramachandran, S.; Newman, M. S. *Org. Synth. Coll. Vol. V*; Wiley: New York, **1973**, 486.

(3) Buchschahcer, P.; Fürst, A.; Gutzwiller, J. *Org. Synth. Coll. Vol. VII*; Wiley: New York, **1990**, 368.

(4) (a) Dauben, W. G.; Hart, D. J. *J. Org. Chem.* **1977**, *42*, 3787. (b) Aav, R.; Kanger, T.; Pehk, T.; Lopp, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180*, 1739.

(5) NakashitaY, ; Watanabe, T.; Benkert, E.; Lorenzi-Riatsch, A.; Hesse, M. *Helv. Chim. Acta* **1984**, *67*, 1204.

(6) Geetha, G.; Raju, N.; Rajagopalan, K.; Swaminathan, S. *Indian J. Chem.* **1981**, *20B*, 238.

(7) Brooks, D. W.; Woods, K. W. *J. Org. Chem.* **1987**, *52*, 2036.

(8) (a) Kinoshita, A.; Mori, M. *Chem. Lett.* **1994**, 1475. (b) Mori, M.; Isono, ; Kaneta, N.; Shibasaki, M. *J. Org. Chem.* **1993**, *58*, 2972.

(9) (a) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1980**, *102*, 5699. (b) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 4929.

(10) 6-Allyl-6-methyldihydro-2*H*-pyran-2,5 (6*H*)-dione: ^{1}H NMR ($CDCl_3$): δ = 5.72 (m, 1 H, =CH), 5.13 and 5.15 (m, 2 H, $=CH_2$), 2.84 and 2.88 (m, 2 H, H-3), 2.73 and 2.60 (m, 2 H, H-4), 2.65 and 2.45 (tdd each, 2 H, *J* = 0.9, 0.9, 7.4, 14.1 Hz, $CH_2CH=CH_2$), 1.48 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$): δ = 207.23 (C-5), 169.24 (C-2), 130.35 (=CH), 121.06 ($=CH_2$), 88.71 (C-6), 43.20 ($CH_2CH=CH_2$), 33.96 (C-4), 28.04 (C-3), 24.92 (CH_3).

(11) Borowitz, I. J.; Parnes, H.; Lord, E.; Yee, K. C. *J. Am. Chem. Soc.* **1972**, *94*, 6817.

(12) Borowitz, I. J.; Grossman, L. J. *Tetrahedron Lett.* **1962**, 471.

(13) Alternatively, a crystalline phosphonium salt can be isolated by filtration remaining by-product into solution. However, this isolation decreases the overall yield of compound **2** from 79% to 64%.

(14) Paju, A.; Kanger, T.; Pehk, T.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2002**, *13*, 2439.

(15) Paju, A.; Kanger, T.; Pehk, T.; Lindmaa, R.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1565.

(16) Paju, A.; Kanger, T.; Niitsoo, O.; Pehk, T.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2003**, *14*, 2393.

(17) Paju, A.; Kanger, T.; Pehk, T.; Eek, M.; Lopp, M. *Tetrahedron* **2004**, *60*, 9081.

(18) (a) Fujita, M.; Shindo, M.; Shishido, K. *Tetrahedron Lett.* **2005**, *46*, 1269. (b) Yao, S.; Johannsen, M.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 118.

(19) Mandelt, K.; Fitjer, L. *Synthesis* **1998**, 1523.

(20) Navarro-Eisenstein, A. M.; Vasquez, P. C.; Franklin, P. J.; Baumstark, A. L. *Heterocycl. Commun.* **2003**, *9*, 449.