Synthesis of Mono- and Sesquiterpenoids; XXIV:[1] (−)-Homogynolide A, an Insect Antifeedant Isolated from *Homogyne alpina*

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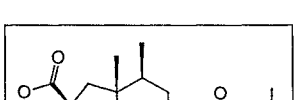
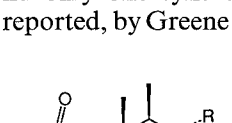
(−)-Homogynolide A (**1**), an insect antifeedant isolated from *Homogyne alpina* (Compositae), was synthesized from (1*R*,4*S*,6*S*)-6-hydroxy-1-methylbicyclo[2.2.2]octan-2-one (**7**), which was readily prepared by the yeast reduction of the corresponding prochiral β-diketone. The key step was the oxy-Cope rearrangement of **6** to give **5**.

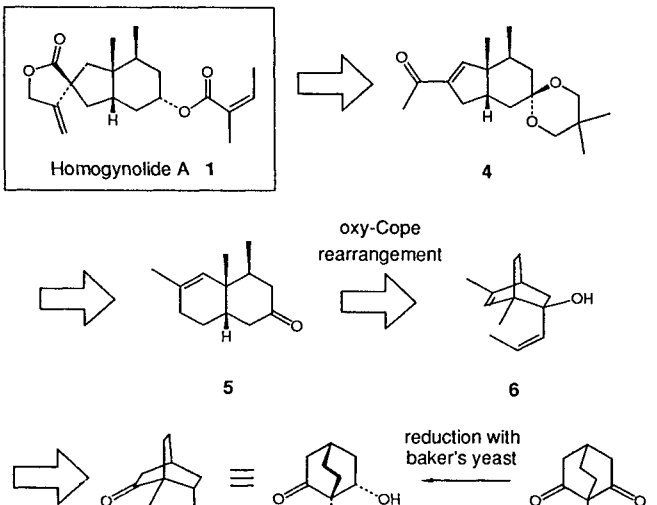
(−)-Homogynolide A (**1**) is a bakkenolide sesquiterpene isolated from *Homogyne alipina* by Harmatha et al. together with bakkenolide A (**2**) and homogynolide B (**3**).[3] It shows antifeedant activity against beetle adults (*Sitophilus granarius, Tribolium confusum*) and larvae (*Trogoderma granarium, Tribolium confusum*), which are pests of stored grains and seeds.[4] This antifeedant activity of **1** prompted us to synthesize the pure and naturally occurring enantiomer of **1**. There are some examples of the syntheses of bakkenolides,[5] and only one synthesis of (−)-homogynolide A has been reported, by Greene et al.[6]





Our retrosynthetic analysis is shown in Scheme 1. We have previously described the microbial reduction of symmetrical bridged β-diketones with baker's yeast.[7-9] The hydroxy ketone **7** with the depicted absolute configuration is obtainable in high enantiomeric purity (99% ee) by reducing the diketone **8**.[7] This hydroxy ketone **7** was employed as the common starting material in our recent syntheses of (+)-pinthunamide[10] and (*E*)-*endo*-bergamoten-12-oic acids.[1] The hydroxy ketone **7** can be converted into **6** in several steps. The key step of the present synthesis is the oxy-Cope rearrangement of **6** to give **5**. The unsaturated six-membered ring of **5** was to be contracted to the five-membered ring to give a hydrindane **4** with the desired three chiral centers. Compound **4** then affords homogynolide A (**1**) through a multistep sequence including the construction of the α-spiro-β-methylene lactone moiety.

The first stage of the synthesis was the preparation of the substrate **6** for oxy-Cope rearrangement[11] as shown in Scheme 2. After the protection of the hydroxy group of **7** as the ethoxyethyl (EE) ether, the resulting product **9** was methylated with methyl iodide and lithium diisopropylamide (LDA) to give **10**. The ketone **10** was then converted into the olefin **12** by employing the Pd-catalyzed reduction[12] of the corresponding enol trifluoromethanesulfonate (triflate = Tf) **11**, which was obtained by

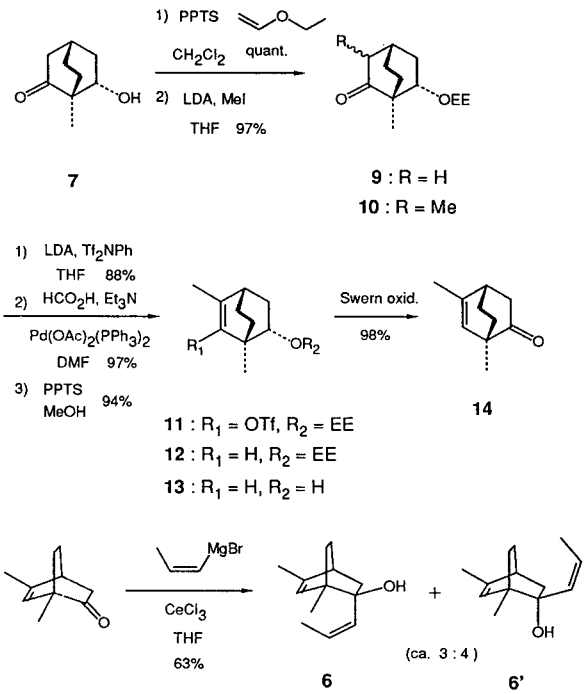


Scheme 1

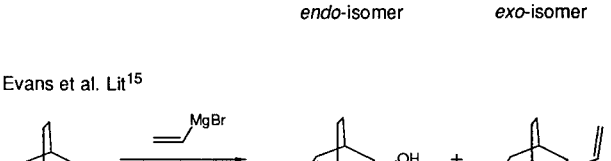
treating the lithium enolate of **10** with *N*-phenyltrifluoromethanesulfonimide ($PhNTf_2$).[13] After the removal of the EE protective group of **12**, the resulting alcohol **13** was oxidized to give the ketone **14**. The next step was the introduction of a *cis*-1-propenyl group. The conventional Grignard reaction resulted in a poor yield. A better alternative was the use of the corresponding cerium reagent[14] prepared in situ, which reacted with **14** to give **6** and **6'** in a moderate yield but with little stereoselectivity affording both *endo*-**6** and *exo*-**6'** in a ratio of ca. 3:4. We originally expected a more desirable ratio of the isomers by analogy to Evan's result in which the substrate was **15** and the ratio of **16** and **16'** was 2:1.[15] Thus, the obtained inseparable mixture of **6** and **6'** was submitted to the next key reaction.

The choice of solvent was the key to the success of the oxy-Cope rearrangement reaction. In refluxing THF no desired product was obtained. When 1,2-dimethoxyethane (DME) was employed, the desired **5** was obtained in only a very low yield (6%, or ca. 14% considering the amount of the non-reacting **6'**). When the solvent was changed to toluene, however, the yield increased to 27% (or ca. 63% considering the amount of the non-reacting **6'**) (Scheme 3). At this stage (compound **5**), three out of the five chiral centers of **1** were arranged with the correct stereochemistry. The carbonyl group of **5** can be reduced stereoselectively in a later stage of this synthesis according to Greene's procedure.[16]

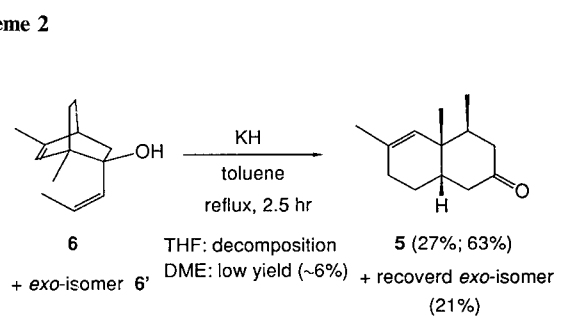
The next stage of the synthesis was the ring contraction of the unsaturated six-membered ring to a five-membered ring. Ozonolysis of **17** followed by the reductive workup



cf. Evans et al. Lit[15]

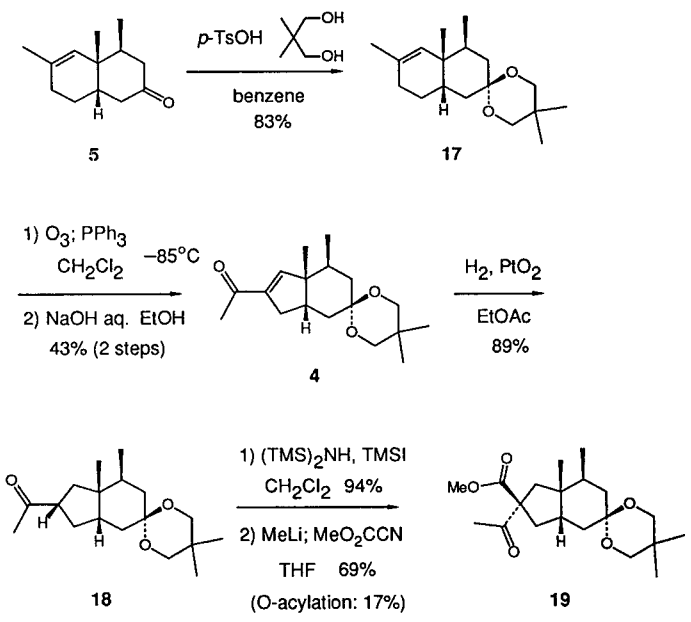


Scheme 2



Scheme 3

with dimethyl sulfide in MeOH at $-78\,^{\circ}C$ failed, giving an undesired keto acid. But reductive workup with triphenylphosphine in CH_2Cl_2 below $-85\,^{\circ}C$ successfully gave the desired keto aldehyde, which was submitted to subsequent aldol condensation to furnish **4** in a moderate yield. The double bond of **4** was then hydrogenated to give a saturated ketone **18** as a single stereoisomer. The stereochemistry as depicted in **18** (Scheme 4) was assigned on the assumption that hydrogenation took place at the less hindered convex side of **4**. To construct the quaternary carbon atom at the spiro center, a methoxycarbonyl group was selectively introduced at that position by treating lithium enolate of **18** with methyl cyanoformate[17] via the thermodynamically more stable silyl enol ether[18] derived from **18**. Fortunately, the reaction was highly stereoselective to give only **19** by the attack of the reagent from the less hindered convex side of **18**.

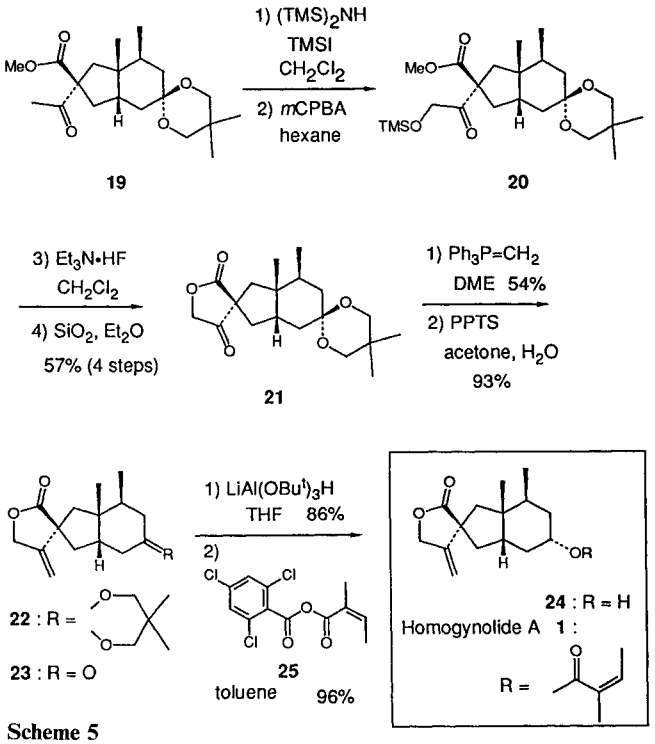


Scheme 4

Conversion of the resulting keto ester **19** into the known keto lactone **23** necessitated the formation of a β-methylene-γ-lactone system. This was successfully achieved by the sequence: (i), introduction of a hydroxy group at the α-position of methyl ketone **19**; (ii), Wittig methylenation of the ketone carbonyl group of **21**; and (iii), removal of the acetal protective group of **22** (Scheme 5). Firstly, the introduction of the hydroxy group was achieved by the epoxidation of the silyl enol ether of **19** with *m*-chloroperbenzoic acid (*m*-CPBA) followed by the rearrangement of the epoxide to give the α-silyloxy ketone **20**.[19] This silyloxy keto ester **20** was desilylated and lactonized on silica gel to give **21**. Wittig olefination of **21** yielded **22**, which was treated with pyridinium *p*-toluenesulfonate (PPTS) in aqueous acetone to give **23**. The obtained intermediate **23** showed spectral data in good agreement with **23** derived from the natural **1**.[3]

The remaining steps leading to **1** have already been reported by Greene et al.,[16,20] and we followed their route: (i), reduction of **23** with lithium tri-*tert*-butoxyaluminium hydride to give **24** as the major product (**24**: its isomer with a β-OH = ca. 9:1, the reported selectivity was > 20:1);[16] and (ii), esterification of **24** with **25** by the modified Yamaguchi procedure.[20] The melting point, specific rotation and the spectroscopic properties (IR, ^1H and ^{13}C NMR) of our synthetic (−)-homogynolide A (**1**) were identical with those of the natural[3] and Greene's synthetic[6,20] **1**, respectively. The overall yield of **1** was 0.63% (22 steps) based on **7**.

All melting and boiling points are uncorrected. NMR spectra were recorded on a JEOL JNM EX-90 spectrometer unless otherwise stated. IR spectra were recorded on a Jasco A-102 spectrometer. Optical rotations were measured on a Jasco DIP-370 polarimeter. Mass spectra were recorded on a JEOL DX-303 spectrometer at 70 eV. Column chromatography was carried out on columns packed with Merck Kieselgel 60, Art. Nr. 7734. Preparative thin layer chromatography was carried out with Merck Kieselgel 60 F_{254} Art. Nr. 5744.



Scheme 5

Compounds **1**, **4**, **5**, **6** and **6'**, **9–13**, **17–19**, and **21–24** gave C, H analysis ± 0.22%; except **6** and **6'**, **10** and **21** gave C ± 0.44%.

(1*R*,4*S*,6*S*)-6-(1-Ethoxyethoxy)-1-methylbicyclo[2.2.2]octan-2-one (9):

To a stirred solution of **7** (6.57 g, 42.6 mmol) in ethyl vinyl ether (100 mL) and CH_2Cl_2 (50 mL) was added PPTS (75 mg, 0.30 mmol) at r.t. and the mixture was stirred for 0.75 h. After addition of sat. aq $NaHCO_3$ (200 mL), the mixture was extracted with Et_2O (2 × 150 mL). The combined extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (silica gel, 200 g; hexane/EtOAc, 7:1) affording **9**; yield: 9.64 g (quant.); $n_D^{17.8}$ 1.4717; $[\alpha]_D^{17.8}$ + 15.2° (*c* = 1.33, $CHCl_3$).

IR (film): $\nu = 1725\ cm^{-1}$ (s, C=O).

^1H NMR ($CDCl_3$/TMS): δ = 0.79–2.72 (m, 13 H, H-4, -5, -7, -8, OCH_2CH_3 and $OCHCH_3O$), 1.04, 1.08 (each s, 3 H, CH_3), 2.28 (br s, 2 H, H-3), 3.37–3.98 (m, 3 H, H-6 and OCH_2CH_3), 4.56–4.93 (m, 1 H, $OCHCH_3O$).

(1*R*,4*R*,6*S*)-6-(1-Ethoxyethoxy)-1,3-dimethylbicyclo[2.2.2]octan-2-one (10):

A solution of LDA in anhydr. THF was prepared by the dropwise addition of BuLi (29.1 mL, 1.61 M in hexane, 46.9 mmol) to a stirred solution of *i*-Pr_2NH (6.87 mL, 49.0 mmol) in anhydr. THF (100 mL) at − 40 to − 50 °C under Ar. To this solution was added a solution of **9** (9.60 g, 42.4 mmol) in anhydr. THF (35 mL) at − 45 to − 50°. The mixture was warmed to 0 °C, stirred for 10 min and cooled again to − 50 °C. MeI (3.40 mL, 93%, 50.7 mmol) was added to the mixture. It was then warmed to 0 °C, poured into sat. aq NH_4Cl (150 mL), and extracted with Et_2O (2 × 150 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (silica gel, 200 g; hexane/EtOAc, 10:1) affording **10**; yield: 9.84 g (97%); $n_D^{17.2}$ 1.4709; $[\alpha]_D^{17.2}$ + 6.93° (*c* = 1.51, $CHCl_3$).

IR (film): $\nu = 1722\ cm^{-1}$ (s, C=O).

^1H NMR ($CDCl_3$/TMS): δ = 0.70–2.43 (m, 17 H, H-4, -4, -5, -7, -8, 3-CH_3, OCH_2CH_3 and $OCHCH_3O$), 0.99, 1.03 (each s, 3 H, 1-CH_3), 3.27–3.96 (m, 3 H, H-6 and OCH_2CH_3), 4.66, 4.81 (each q, 1 H, *J* = 5.3 Hz, $OCHCH_3O$).

(1*R*,4*S*,6*S*)-6-(1-Ethoxyethoxy)-1,3-dimethyl-2-trifluoromethanesulfonyloxybicyclo[2.2.2]oct-2-ene (11):

A solution of LDA in anhydr. THF was prepared by the dropwise addition of BuLi (6.33 mL, 1.71 M in hexane, 10.8 mmol) to a stirred solution of *i*-Pr_2NH (1.57 mL, 11.3 mmol) in anhydr. THF (60 mL) at − 50 to − 60 °C under Ar. To this solution was added a solution of **10** (2.00 g, 8.32 mmol) in anhydr. THF (16 mL) at − 60 to − 70 °C. The mixture was warmed to 0 − 10 °C, stirred for 10 min, and cooled again to − 70 °C. $PhNTf_2$ (3.57 g, 9.99 mmol) was added to the mixture, and after 0.5 h the mixture was warmed to 0 °C, poured into sat. aq $NaHCO_3$ (150 mL), and extracted with Et_2O (3 × 100 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (silica gel, 90 g; hexane/Et_2O, 20:1) affording **11**; yield: 2.73 g (88%); $n_D^{18.2}$ 1.4419; $[\alpha]_D^{18.2}$ − 3.25° (*c* = 1.02, $CHCl_3$).

IR (film): $\nu = 1685$ (s, C=C), 1405, 1212, 1142, 1078, 880 cm^{-1} (OSO_2).

^1H NMR ($CDCl_3$): δ = 0.87–2.19 (m, 15 H, H-5, -7, -8, 1-CH_3, OCH_2CH_3 and $OCHCH_3O$), 1.88 (s, 3 H, 3-CH_3), 2.52 (br s, 1 H, H-4), 3.29–3.74 (m, 3 H, H-6 and OCH_2CH_3), 4.70 (br q, 1 H, *J* = 5.4 Hz, $OCHCH_3O$).

(1*S*,4*S*,6*S*)-6-(1-Ethoxyethoxy)-1,3-dimethylbicyclo[2.2.2]oct-2-ene (12):

To a solution of **11** (2.73 g, 7.34 mmol), Et_3N (3.83 mL, 27.5 mmol) and $Pd(OAc)_2(PPh_3)_2$ (142 mg, 0.190 mmol) in DMF (45 mL) was added formic acid (692 µL, 18.3 mmol) and the mixture was stirred at 50–60 °C for 40 min. The mixture was poured into H_2O (50 mL) and extracted with Et_2O (3 × 100 mL). The combined organic solution was washed with H_2O (50 mL), sat. aq $NaHCO_3$ (50 mL), brine (30 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (silica gel, 40 g); hexane/Et_2O, 30:1) affording **12**; yield: 1.60 g (97%); $n_D^{18.5}$ 1.4635; $[\alpha]_D^{18.5}$ − 6.51° (*c* = 1.23, $CHCl_3$).

IR (film): $\nu = 1650\ cm^{-1}$ (w, C=C).

^1H NMR ($CDCl_3$/TMS): δ = 0.72–2.18 (m, 15 H, H-5, -7, -8, 1-CH_3, OCH_2CH_3 and $OCHCH_3O$), 1.80 (d, 3 H, *J* = 1.1 Hz, 3-CH_3), 2.28 (br s, 1 H, H-4), 3.21–3.86 (m, 3 H, H-6 and OCH_2CH_3), 4.70 (q, 1 H, *J* = 5.5 Hz, $OCHCH_3O$), 5.47 (br s, 1 H, H-2).

(1*S*,2*S*,4*S*)-1,5-Dimethylbicyclo[2.2.2]oct-5-en-2-ol (13):

To a stirred solution of **12** (6.49 g, 28.9 mmol) in MeOH was added pyridinium *p*-toluenesulfonate (0.50 g, 1.99 mmol) at r.t. and the mixture was stirred for 16 h. $NaHCO_3$ (5 g) was added, the mixture was filtered through Celite and concentrated in vacuo at 0 °C. The residue was diluted by Et_2O, filtered through SiO_2 and again concentrated in vacuo at 0 °C. The residue was recrystallized from hexane to give pure **13** (3.48 g) as colorless needles. Additional **13** (0.66 g) was gained from the mother liquor by chromatography; yield: 4.14 g (94%); mp 90.5–92.0 °C; $[\alpha]_D^{18.3}$ − 50.4° (*c* = 1.21, $CHCl_3$).

IR ($CHCl_3$): $\nu = 3580$ (w, monomeric OH), 3250 (br w, OH), 1630 cm^{-1} (br w, C=C).

^1H NMR ($CDCl_3$/TMS): δ = 0.77–2.22 (m, 6 H, H-3, -7, -8), 1.18 (s, 3 H, 1-CH_3), 1.82 (d, 3 H, *J* = 1.7 Hz, 5-CH_3), 2.32 (br s, 1 H, H-4), 3.37–3.64 (m, 1 H, H-2), 5.41 (br d, 1 H, *J* = 1.7 Hz, H-6).

(1*S*,2*S*,4*S*)-1,5-Dimethylbicyclo[2.2.2]oct-5-en-2-one (14):

A solution of the Swern reagent was prepared by the dropwise addition of DMSO (3.27 mL, 45.7 mmol) to a stirred solution of $(COCl)_2$ (2.59 mL, 29.7 mmol) in anhydr. CH_2Cl_2 (70 mL) at − 55 to − 65 °C under Ar. To this solution was added dropwise a solution of **13** (3.48 g, 22.9 mmol) in anhydr. CH_2Cl_2 (25 mL) at − 60 to − 70 °C. The mixture was stirred for 1 h and treated with Et_3N (12.7 mL, 91.1 mmol). The temperature was allowed to rise gradually to 0 °C over 1 h. The mixture was poured into H_2O (100 mL) and extracted with Et_2O (2 × 100 mL). The combined ether solution was washed with sat. aq $NaHCO_3$ (100 mL), brine (100 mL), dried ($MgSO_4$), filtered through SiO_2 and concentrated in vacuo at 0 °C.

The residue was distilled under reduced pressure to afford **14**; yield: 3.35 g (98%); bp 103–105 °C/23 mmHg; $n_D^{18.3}$ 1.4868; $[\alpha]_D^{18.3}$ −443° (c = 1.31, $CHCl_3$).

HRMS: Calc. for $C_{10}H_{14}O$, 150.1045; found 150.1027.

IR (film): ν = 1723 cm^{-1} (s, C=O).

^1H NMR ($CDCl_3$/TMS): δ = 0.68–2.30 (m, 4H, H-7, -8), 1.18 (s, 3H, 1-CH_3), 1.84 (d, 3H, J = 1.7 Hz, 5-CH_3), 2.06 (d, 2H, J = 2.6 Hz, H-3), 2.67 (br s, 1H, H-4), 5.45 (br s, 1H, H-6).

(1*S*,2*RS*,4*S*)-1,5-Dimethyl-2-[(*E*)-1-propenyl]bicyclo[2.2.2]oct-5-en-2-ol (6 and 6′):

A solution of the Grignard reagent was prepared by heating a suspension of Mg (turnings, 0.121 g, 4.98 mmol) in *cis*-1-bromopropene (0.51 mL, 5.95 mmol) and anhydr. THF (6 mL) under Ar. To the suspension of anhydr. $CeCl_3$ in anhydr. THF (15 mL) (previously prepared in another flask 15 h, before) was added a solution of **14** (150 mg, 0.999 mmol) at r.t. under Ar. The mixture was stirred for 0.5 h. and cooled to 0 °C. To this stirred mixture was added dropwise the Grignard reagent (5 mL). The mixture was stirred at 0 °C for 3.5 h, at r.t. for 0.5 h, poured into sat. aq NH_4Cl (50 mL) and extracted with Et_2O (2 × 50 mL). The combined extracts were washed with sat. aq $NaHCO_3$ (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (silica gel, 15 g; hexane/Et_2O, 30:1) affording a mixture of **6** and **6′**; yield: 121 mg (63%); $n_D^{18.7}$ 1.5042; $[\alpha]_D^{18.7}$ −62° (c = 0.22, $CHCl_3$).

IR (film): ν = 3490 (br w, OH), 1643 cm^{-1} (br w, C=C).

^1H NMR ($CDCl_3$/TMS): δ = 0.70–2.47 (m, 13H, H-3, -4, -7, -8, 5-CH_3 and C=CHCH_3), 1.05, 1.15 (each s, 3H, 1-CH_3), 5.28–5.70 (m, 3H, H-6 and CH=CH).

(1*R*,2*R*,6*R*)-1,2,9-Trimethylbicyclo[4.4.0]dec-9-en-4-one (5):

KH (1.20 g, 20% suspension in mineral oil) was washed with anhydr. toluene (2 × 5 mL) and suspended in anhydr. toluene (30 mL) under Ar. To the suspension was added a solution of **6** and **6′** (399 mg, 2.07 mmol) and the mixture was refluxed for 2.5 h. The reaction mixture was cooled, quenched with ice-cooled H_2O (20 mL), poured into sat. aq NH_4Cl (50 mL), and extracted with Et_2O (2 × 50 mL). The combined ether solution was washed with sat. aq $NaHCO_3$ (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (silica gel, 50 g; hexane/Et_2O, 30:1) affording **5** [the isomer **6′** (84 mg, 21%) was recovered]; yield: 107 mg (27%); $n_D^{18.3}$ 1.5051; $[\alpha]_D^{18.3}$ −44.0° (c = 1.05, $CHCl_3$).

IR (film): ν = 1712 cm^{-1} (s, C=O).

^1H NMR ($CDCl_3$/TMS): δ = 0.64–2.43 (m, 8H, H-2, -3, -5, -6, -7), 0.93 (d, 3H, J = 5.4 Hz, 2-CH_3), 1.10 (s, 3H, 1-CH_3), 1.67 (s, 3H, 9-CH_3), 2.58 (br dd, 2H, J = 5.4, 13.5 Hz, H-8), 5.31 (br s, 1H, H-10).

(1*R*,6*S*,10*R*)-8-(2,2-Dimethyltrimethylenedioxy)-1,3,10-trimethylbicyclo[4.4.0]dec-2-ene (17):

To a solution of **5** (204 mg, 1.06 mmol) and 2,2-dimethyl-1,3-propanediol (0.59 g, 5.66 mmol) in anhydr. benzene (10 mL) was added PPTS (20 mg, 0.105 mmol), and the mixture was refluxed for 0.25 h with a side-arm dropping funnel packed with MS 4A to remove water. The mixture was cooled, poured into sat. aq $NaHCO_3$ (30 mL) and extracted with Et_2O (2 × 50 mL). The ether solution was washed with brine (30 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (silica gel, 10 g; hexane/Et_2O, 50:1) affording **17**; yield: 243 mg (83%); $n_D^{18.3}$ 1.4978;; $[\alpha]_D^{18.3}$ +16° (c = 0.30, $CHCl_3$).

IR (film): ν = 1640 (br w, C=C), 1110 cm^{-1} (s, C–O).

^1H NMR ($CDCl_3$/TMS): δ = 0.70–2.33 (m, 10H, H-4, -5, -6, -7, -9, -10), 0.86 (d, 3H, J = 7.2 Hz, 10-CH_3), 0.90 (s, 6H, CCH_3), 1.02 (s, 3H, 1-CH_3), 1.63 (br s, 3H, 3-CH_3), 3.29–3.73 (m, 4H, OCH_2), 5.25 (br s, 1H, 2-H).

(1*R*,2*R*,6*S*)-8-Acetyl-4-(2,2-dimethyltrimethylenedioxy)-1,2-dimethylbicyclo[4.3.0]non-8-ene (4):

Into a solution of **17** (137 mg, 0.493 mmol) in anhydr. CH_2Cl_2 (25 mL) was bubbled ozone gas at below −85 °C until the color of the solution turned blue. After the removal of excess ozone with bubbling N_2 gas, a solution of triphenylphosphine (155 mg, 0.592 mmol) in anhydr. CH_2Cl_2 (3 mL) was added to the mixture at below −85 °C and the temperature was allowed to rise gradually to r.t. over 2 h. The reaction mixture was concentrated in vacuo and the resulting crude keto aldehyde (ν = 1715 cm^{-1}) was immediately dissolved with 95% EtOH (10 mL). To the mixture was added 15% aq NaOH (3.5 mL, 1.3 mmol) at 0 °C and the mixture was stirred at r.t. for 4 h. The reaction mixture was extracted with Et_2O (2 × 30 mL). The combined ether solution was washed with H_2O (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by thin layer silica gel chromatography (hexane/EtOAc, 10:1) to give **4**; yield: 62.1 mg (43%); $n_D^{19.4}$ 1.4986; $[\alpha]_D^{19.4}$ −24.6° (c = 1.36, $CHCl_3$).

IR (film): ν = 1663 (s, C=O), 1603 cm^{-1} (s, C=C).

^1H NMR ($CDCl_3$): δ = 0.89 (d, 3H, J = 5.4 Hz, 2-CH_3), 0.90 (s, 3H, CCH_3), 1.01 (s, 3H, CCH_3), 1.04 (s, 3H, 1-CH_3), 1.13–2.49 (m, 6H, H-2, -3, -5, -6), 2.27 (s, 3H, CH_3C=O), 2.49–2.75 (m, 2H, H-7), 3.20–3.74 (m, 4H, OCH_2), 6.65 (br s, 1H, H-9).

(1*R*,2*R*,6*S*,8*S*)-8-Acetyl-4-(2,2-dimethyltrimethylenedioxy)-1,2-dimethylbicyclo[4.3.0]nonane (18):

To a solution of **4** (93.6 mg, 0.320 mmol) in EtOAc (10 mL) was added PtO_2 (17.2 mg, 7.57×10^{-2} mmol) and the suspension was stirred at r.t. for 0.25 h under H_2. The reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (5 g). Elution with hexane/Et_2O (6:1) gave **18**; yield: 83.7 mg (89%); $n_D^{18.4}$ 1.4877; $[\alpha]_D^{18.4}$ −15.4° (c = 1.41, $CHCl_3$).

IR (film): ν = 1710 cm^{-1} (s, C=O).

^1H NMR ($CDCl_3$/TMS): δ = 0.84 (d, 3H, J = 6.3 Hz, 2-CH_3), 0.90 (s, 3H, CCH_3), 0.93 (s, 3H, CCH_3), 0.96 (s, 3H, 1-CH_3), 1.00–2.52 (m, 10H, H-2, -3, -5, -6, -7, -9), 2.12 (s, 3H, CH_3C=O), 2.66–3.03 (m, 1H, H-8), 3.45 (s, 2H, OCH_2), 3.49 (s, 2H, OCH_2).

Methyl (1*R*,2*R*,6*S*,8*R*)-8-Acetyl-4-(2,2-dimethyltrimethylenedioxy)-1,2-dimethylbicyclo[4.3.0]nonane-8-carboxylate (19):

To a solution of **18** (83.7 mg, 0.284 mmol) and $(TMS)_2NH$ (300 µL, 1.42 mmol) in anhydr. CH_2Cl_2 (8 mL) was added dropwise TMSI (101 µL, 0.710 mmol) at −22 °C and the mixture was stirred at −4 °C for 20 min. The reaction mixture was slowly added dropwise to a stirred mixture of pentane (10 mL) and sat. aq $NaHCO_3$ (30 mL) at 0 °C and extracted with pentane (2 × 30 mL). The combined pentane solution was washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was quickly chromatographed (silica gel, 5 g; hexane/Et_2O, 10:1) affording 98.0 mg (94%) of the silyl enol ether (ν = 1692 cm^{-1}). This was immediately used for the next step without further purification.

To the solution of silyl enol ether (98 mg, 0.266 mmol) in anhydr. THF (8 mL) was added dropwise MeLi (500 µL, 1.09 M in Et_2O, 0.545 mmol) at −18.5 to −19 °C. The mixture was stirred for 0.5 h and cooled to −73 to −74.5 °C. Then, methyl cyanoformate (58 µL, 0.73 mmol) in anhydr. THF (0.8 mL) was added dropwise to the mixture. The temperature was allowed to rise to −10 °C. The reaction mixture was poured into ice-cooled H_2O (30 mL), and extracted with Et_2O (2 × 30 mL). The combined ether solution was washed with sat. aq $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (silica gel, 13 g; hexane/Et_2O, 10:1) affording **19**; yield: 64.2 mg (69%, 2 steps); An analytical sample was obtained as colorless needles by recrystallization from hexane; mp 81.5–82.5 °C; $[\alpha]_D^{21.3}$ +58.4° (c = 1.01, $CHCl_3$).

IR ($CHCl_3$): ν = 1735 (br w, ester C=O), 1710 cm^{-1} (s, ketone C=O).

^1H NMR ($CDCl_3$/TMS): δ = 0.86 (d, 3H, J = 6.8 Hz, 2-CH_3), 0.93 (s, 6H, CCH_3), 0.98 (s, 3H, 1-CH_3), 1.04–2.75 (m, 10H, H-2, -3, -5, -6, -7, -9), 2.01 (s, 3H, CH_3C=O), 3.45 (br s, 2H, OCH_2), 3.50 (br s, 2H, OCH_2), 3.72 (s, 3H, OCH_3).

(1′*R*,2′*R*,6′*S*,8′*R*)-4′-(2,2-Dimethyltrimethylenedioxy)-1′,2′-dimethylspiro{3-oxacyclopentane-1,8′-bicyclo[4.3.0]nonane}-2,5-dione (21):

To a solution of **19** (232 mg, 0.658 mmol) and $(TMS)_2NH$ (0.85 mL, 4.0 mmol) in anhydr. CH_2Cl_2 (10 mL) was added dropwise TMSI (281 μL, 1.98 mmol) at −19 °C and the mixture was stirred at r.t. for 2 h. The reaction mixture was slowly added dropwise to a stirred mixture of pentane (10 mL) and sat. aq $NaHCO_3$ (50 mL) at 0 °C and extracted with pentane (2 × 50 mL). The combined pentane solution was washed with H_2O (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The obtained crude silyl enol ether (ν = 1615 cm^{-1}) was immediately used for the next step without purification.

To a suspension of *m*-CPBA (157 mg, 80%, 0.729 mmol) in anhydr. hexane (5 mL) was added dropwise the crude silyl enol ether in anhydr. hexane (7 mL) at −16 °C. The reaction mixture was stirred at below 3 °C for 4 h, filtered through Celite and concentrated in vacuo. The obtained crude silyl ether was immediately used for the next step without purification.

To a solution of the crude silyl ether in anhydr. CH_2Cl_2 (10 mL) was added $Et_3N \cdot HF$ (0.20 g, 1.65 mmol) at −22 °C. The mixture was stirred at below 3 °C for 1 h, and to the mixture was added sat. aq $NaHCO_3$ (30 mL) and 10% aq $Na_2S_2O_4$ (5 mL). After stirring for 0.5 h, at r.t., the mixture was extracted with Et_2O (50 mL, 2 × 20 mL). The combined ether solution was washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The obtained crude hydroxy ketone (ν = 3420, 1715 cm^{-1}) was immediately used for the next step without purification.

To a solution of the hydroxy ketone in Et_2O (10 mL) was added silica gel (8 g). The mixture was stirred for 10 h at r.t., filtered through Celite and the filtrate was concentrated in vacuo. The residue was chromatographed (silica gel, 20 g; hexane/Et_2O, 5:1) affording **21** as a foam; yield: 126 mg (57%); mp 43.5–52.0 °C, $[\alpha]_D^{21.8}$ −19.8° (*c* = 0.875, $CHCl_3$).

IR ($CHCl_3$): ν = 1802 (w, lactone C=C), 1758 cm^{-1} (s, ketone C=O).

^1H NMR ($CDCl_3$/TMS): δ = 0.88 (d, 3 H, *J* = 6.8 Hz, 2′-CH_3), 0.92 (s, 3 H, CCH_3), 0.97 (s, 3 H, CCH_3), 1.02 (s, 3 H, 1′-CH_3), 1.08–2.82 (m, 10 H, H-2′, -3′, -5′, -6′, -7′, -9′), 3.43 (s, 2 H, OCH_2), 3.51 (s, 2 H, OCH_2), 4.60 (s, 2 H, H-4).

(1′*R*,2′*R*,6′*S*,8′*R*)-4′-(2,2-Dimethyltrimethylenedioxy)-1′,2′-dimethyl-5-methylenespiro{3-oxacyclopentane-1,8′-bicyclo[4.3.0]nonan}-2-one (22):

A solution of the salt-free Wittig reagent was prepared by the dropwise addition of BuLi (1.05 mL, 1.60 M in hexane, 1.68 mmol) to a suspension of triphenylphosphonium bromide (0.70 g, 1.96 mmol) in anhydr. 1,2-dimethoxyethane (DME) (18 mL) at −18 °C under Ar. The mixture was stirred at −10 to −12 °C for 1 h and stored at −20 °C. The obtained supernatant liquid of the Wittig reagent (2 mL) was added dropwise to a solution of **21** (15.2 mg, 4.51 × 10^{-2} mmol) in anhydr. DME (1 mL) at −9.5 °C under Ar. The reaction mixture was stirred at 0 °C for 1 h, poured into H_2O (30 mL) and extracted with Et_2O (2 × 30 mL). The combined ether solution was washed with sat. aq $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (silica gel; 6 g; hexane/EtOAc, 7:1) affording **22**; yield: 8.1 mg (54%). An analytical sample was obtained as colorless rods by recrystallization from hexane; mp 113.2–115.0 °C; $[\alpha]_D^{21.8}$ −19.8° (*c* = 0.875, $CHCl_3$).

IR ($CHCl_3$): ν = 1770 (s, C=O), 1673 cm^{-1} (w, C=CH_2).

^1H NMR ($CDCl_3$/TMS): δ = 0.87 (s, 3 H, CCH_3), 0.91 (d, 3 H, *J* = 6.3 Hz, 2′-CH_3), 1.02 (s, 3 H, CCH_3), 1.06 (s, 3 H, 1′-CH_3), 1.15–2.59 (m, 10 H, H-2′, -3′, -5′, -6′, -7′, -9′), 3.26–3.76 (m, 4 H, OCH_2), 4.70–4.84 (m, 2 H, H-4), 4.95–5.06 (m, 1 H, C=CHH), 5.06–5.17 (m, 1 H, C=CHH).

(1′*R*,2′*R*,6′*S*,8′*R*)-1′,2′-Dimethyl-5-methylenespiro{3-oxacyclopentane-1,8′-bicyclo[4.3.0]nonane}-2,4′-dione (23):

To a solution of **22** (85.0 mg, 0.254 mmol) in H_2O (0.5 mL) and acetone (22 mL), PPTS (11.7 mg, 4.65 × 10^{-2} mmol) was added and the reaction mixture was refluxed for 9 h. After cooling, the mixture was concentrated in vacuo in the presence of $NaHCO_3$. The residue was diluted with Et_2O, filtered through Celite and the filtrate was concentrated in vacuo. The resulting crude product was chromatographed (silica gel, 10 g; hexane/Et_2O, 3:1) affording **23**; yield: 59.0 mg (93%); $n_D^{19.3}$ 1.5164; $[\alpha]_D^{19.3}$ −10.6° (*c* = 0.640, $CHCl_3$) {Lit.[6] $[\alpha]_D^{25}$ −5°}.

IR (film): ν = 1770 (s, lactone C=C), 1712 (s, ketone C=O), 1670 cm^{-1} (w, C=CH_2).

^1H NMR (500 MHz, JEOL α-500; $CDCl_3$/TMS): δ = 1.00 (d, 3 H, *J* = 6.5 Hz, 2′-CH_3), 1.22 (s, 3 H, 1′-CH_3), 1.73 (t, 3 H, *J* = 13.5 Hz, H-6′), 2.03 (d, 1 H, *J* = 14.0 Hz, one of H-9′), 2.04–2.32 (m, 5 H, H-2′, -3′, -7′), 2.12 (d, 1 H, *J* = 14.0 Hz, one of H-9′), 2.61 (dd, 1 H, *J* = 6.5, 14.5 Hz, one of H-5′), 2.73 (ddt, 1 H, *J* = 2.4, 6.7, 13.4 Hz, one of H-5′), 4.76 (dt, 1 H, *J* = 2.1, 12.8 Hz, one of H-4), 4.79 (dt, 1 H, *J* = 2.1, 12.8 Hz), 5.04–5.07 (m, 2 H, C=CH_2).

(1′*R*,2′*R*,4′*S*,6′*S*,8′*R*)-4′-Hydroxy-1′,2′-dimethyl-5-methylenespiro-{3-oxacyclopentane-1,8′-bicyclo[4.3.0]nonan}-2-one (24):

To a solution of **23** (56.0 mg, 0.226 mmol) in anhydr. THF (10 mL) was added dropwise $LiAl(OBu\text{-}t)_3H$ (1.30 mL, 0.49 M in THF, 0.637 mmol) at −8 °C under Ar. The reaction mixture was stirred at −2 °C for 2 h, quenched by the addition of 0.5 N aq HCl (10 mL), poured into 0.5 N aq HCl (10 mL) and extracted with Et_2O (2 × 50 mL). The combined ether solution was washed with sat. aq $NaHCO_3$ (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed (silica gel, 10 g; hexane/EtOAc, 5:2) affording **24** along with 5.5 mg (9.7%) of its β-epimer; yield: 48.8 mg (86%). An analytical sample was obtained as colorless needles by recrystallization from hexane; mp 93.0–93.6 °C [Lit.[3] (a sample derived from natural **1**) mp 91–93 °C, Lit.[6] (synthetic sample by Greene et al.) mp 91–93 °C]; $[\alpha]_D^{19.2}$ −8.68° (*c* = 0.965, $CHCl_3$) {Lit.[6] $[\alpha]_D^{25}$ −4°}.

IR ($CHCl_3$): ν = 3620 (w, monomeric OH), 3300 (br w, OH), 1765 (s, C=O), 1670 cm^{-1} (w, C=CH_2).

^1H NMR ($CDCl_3$/TMS): δ = 0.89 (d, 3 H, *J* = 6.3 Hz, 2′-CH_3), 0.99 (s, 3 H, 1′-CH_3), 1.07–2.87 (m, 11 H, H-2′, -3′, -5′, -6′, -7′, -9′), 4.03–4.22 (br s, 1 H, H-4′), 4.68–4.84 (m, 2 H, H-4), 4.96–5.08 (m, 1 H, C=CHH), 5.08–5.22 (m, 1 H, C=CHH).

(1′*R*,2′*R*,4′*S*,6′*S*,8′*R*)-1′,2′-Dimethyl-5-methylene-2-oxospiro{3-oxacyclopentane-1,8′-bicyclo[4.3.0]nonane}-4′-yl (*Z*)-2-Methylbut-2-enoate (Homogynolide A) (1):

A solution of the mixed anhydride **25** was prepared by the dropwise addition of 2,4,6-trichlorobenzoyl chloride (201 μL, 1.29 mmol) and Et_3N (179 μL, 1.29 mmol) to a solution of (*Z*)-2-methylbut-2-enoic acid (139 mg, 1.39 mmol) in anhydr. toluene (1 mL) below 20 °C. The mixture was stirred at r.t. for 2 h. To this mixture was added a solution of **24** (46.0 mg, 0.184 mmol) in anhydr. toluene (2.5 mL) and the reaction mixture was stirred at ca. 70 °C for 26 h. After cooling, the mixture was diluted with Et_2O (15 mL), filtered through Celite and the filtrate was concentrated in vacuo. The residue was chromatographed (silica gel, 20 g; hexane/EtOAc, 8:1) affording **1**; yield: 58.9 mg (96%); An analytical sample (48.2 mg) was obtained as colorless needles by recrystallization from hexane; mp 63.5–65.0 °C [Lit.[3] (natural) mp 62–65 °C, Lit.[6] (synthetic) mp 62–64 °C]; $[\alpha]_D^{9.2}$ −27.1° (*c* = 1.14, $CHCl_3$) {Lit.[6] $[\alpha]_D^{25}$ −22°}.

IR ($CHCl_3$): ν = 1770 (s, C=O), 1710 (s, C=O), 1670 (w, C=CH_2), 1645 cm^{-1} (w, C=C).

^1H NMR (500 MHz, JEOL α-500; $CDCl_3$/TMS): δ = 0.90 (d, 3 H, *J* = 6.5 Hz, 2′-CH_3), 1.02 (s, 3 H, 1′-CH_3), 1.51 (ddd, 1 H, *J* = 2.9, 12.6, 15.5 Hz, one of H-3′ or H-5′), 1.69–1.74 (m, 1 H, H-2′), 1.79–1.96 (m, 3 H, H-3′ and H-5′ except one H-5′ or H-3′), 1.85 (br s, 3 H, side chain CCH_3), 1.99 (dd, 3 H, *J* = 1.0, 7.5 Hz, side chain =CHCH_3), 2.03 (br s, 2 H, H-9′), 2.11 (dd, 1 H, *J* = 6.3, 12.8 Hz, one of H-7′), 2.30–2.35 (m, 1 H, H-6′), 2.44 (t, 1 H, *J* = 13.3 Hz, one of H-7′), 4.76 (dt, 1 H, *J* = 2.2, 12.8 Hz, one of H-4), 4.79 (dt, 1 H, *J* = 2.2, 12.8 Hz, one of H-4), 5.03 (s, 1 H, C=CHH), 5.10 (t, 1 H, *J* = 2.3 Hz, C=CHH), 5.17 (quint, 1 H, *J* = 3.0 Hz, H-4′), 6.05 (qq, 1 H, *J* = 1.0, 7.5 Hz, side chain =C*H*CH_3).

^{13}C NMR (125 NHz, JEOL α-500; $CDCl_3$): $\delta = 15.7$ (C), 15.9 (C), 18.8 (C), 20.9 (C), 27.3 (C), 28.6 (C), 34.2 (C), 43.5 (C), 44.60 (C), 44.65 (C), 48.7 (C), 49.7 (C), 69.6 (C), 70.3 (C), 105.6 (C), 127.9 (C), 138.3 (C), 150.4 (C), 167.1 (C), 182.5 (C).

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