First Total Synthesis and Determination of the Absolute Configuration of the Stress Factor (+)-Hydroxymyoporone

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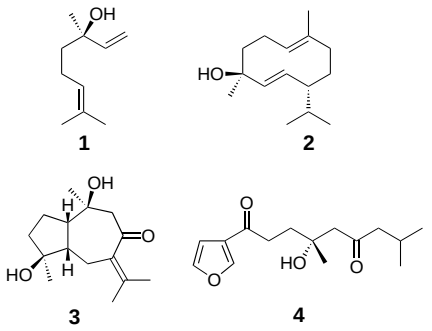
Abstract: The first total synthesis of the stress factor (+)-hydroxymyoporone (**4**) is presented. The key step is an asymmetric allylation of the methyl ketone **10** which proceeds with excellent selectivity and yield. In addition, it was proven that the assignment of the absolute configuration of hydroxymyoporone published in the literature is incorrect; the correct structure of the (+)-enantiomer is depicted in the structural formula **4**.

Keywords: allylation · asymmetric synthesis · natural products · sesquiterpenes

Introduction

A common structural feature of many natural products is a tertiary alcohol moiety with a methyl group as one of the substituents. It can be assumed that this functionality is formed in the biosynthesis by a selective oxidation of an alkene moiety containing a methyl group, which is often encountered in terpenes. Thus, the simple monoterpene linalool (**1**)[1] and also the more complex sesquiterpene hydroxymyoporone (**4**),[2] nephthenol (**2**),[3] and isozedoarondiol (**3**),[4] as well as several macrocyclic cembranoids belong



1 **2** **3** **4**

to this class; in addition, many macrocyclic antibiotics such as erythromycin[5] contain a tertiary alcohol group. However, in the past the enantioselective formation of this characteristic feature caused severe problems and could only be accomplished either by an asymmetric oxidation of the corresponding alkene[6] with subsequent reductive removal of one of the formed hydroxy groups, or by an enantioselective formation of an oxirane with subsequent ring opening. In the preparation of complex molecules both ways proved to be rather difficult. Thus, on the one hand the stereoselective synthesis of trisubstituted alkenes is not without problems, and on the other hand the reductive opening of an epoxide or the removal of a hydroxy group are critical steps;[7] in addition, the oxidations do not always proceed with good enantioselectivity.

Recently, we have presented a highly efficient method for the asymmetric synthesis of tertiary homoallylic alcohols from ketones and allylsilanes such as **6** with very high *ee* values.[8] In this transformation a ketone such as **5** reacts with allyltrimethylsilane (**6**) in the presence of the norpseudoephedrine derivative **7** and catalytic amounts of trifluoromethanesulfonic acid (TfOH) to form a homoallylic benzyl ether **8** (Scheme 1). Subsequent deprotection with sodium in liquid ammonia yields the tertiary homoallylic alcohol **9**; with the parent compound ethyl methyl ketone (**5**) as the most difficult task, the tertiary alcohol **9** is obtained with 92% *ee*. However, the benzyl ether functionality in **8** can also be used as a protecting group for further transformations and can be removed at a later stage.

Herein we describe the total synthesis of the enantiopure (+)-hydroxymyoporone (**4**) with the described asymmetric allylation of a ketone as a key step. (+)-Sesquiterpene **4** is a stress metabolite which is produced by sweet potatoes infected with *Fusarium solani*[2] and possesses a strong lung toxic effect.[9] In addition, hydroxymyoporone was isolated from *Athanasia grandiceps* assuming that the obtained compound is the enantiomer of **4**. However, the determination of the absolute configuration of both compounds seems rather questionable, since the optical rotation of the product isolated from sweet potatoes was never published. Further evidence was obtained only by chemical transformations to other sesquiterpenes of uncertain absolute configuration.

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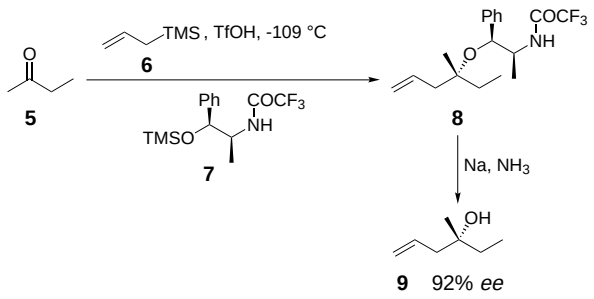
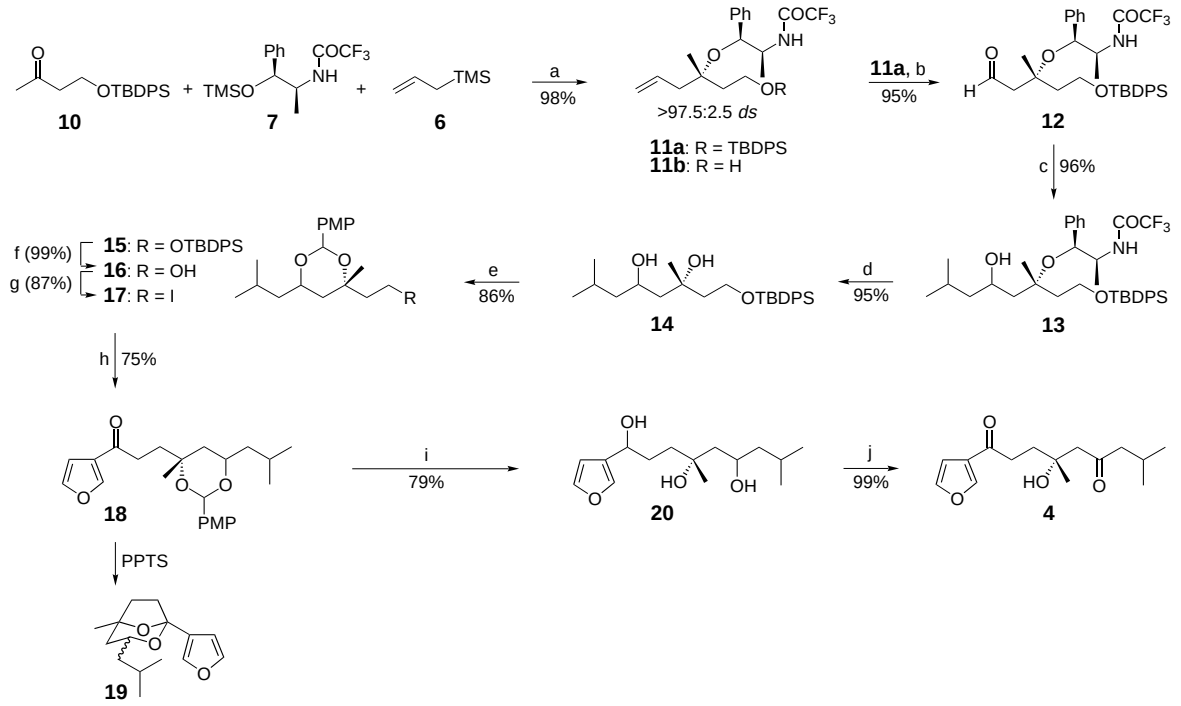


Scheme 1. Enantioselective synthesis of tertiary alcohols by asymmetric allylation of ketones.

Results and Discussion

The retrosynthetic analysis of (+)-hydroxymyoporone (**4**) called for the stereoselective formation of the side chain with the asymmetric allylation of the *tert*-butyldiphenylsilyl (TBDPS) protected β-hydroxybutanone (**10**) as the key step, followed by removal of one carbon, the addition of the isobutyl group, and the introduction of the furan moiety in the last stage of the synthesis with an "umgepolten" furan-3-carbaldehyde as a nucleophile (Scheme 2). The asymmetric allylation of **10** was performed in a domino reaction[10] with allylsilane **6** in the presence of **7** and catalytic amounts of TfOH to give the homoallylic ether **11a** with 98% yield and a remarkable diastereoselectivity of >97.5:2.5.[8, 11] For the determination of the absolute configuration of **11a** an X-ray structural analysis of the crystalline alcohol **11b** was performed,[12] which was easily obtained from **11a** by removal of the silyl ether moiety with tetrabutylammonium fluoride in quantitative yield.[8] The oxidative cleavage of the double bond in **11a** with ozone at $-78\,^{\circ}C$ and triphenylphosphane as the reductant led to the aldehyde **12** in 95% yield, which was transformed into the alcohol **13** as a 1:1 mixture of the two possible diastereomers by using isobutylmagnesium chloride in 96% yield. The low stereoselectivity of this reaction is insignificant, since in the course of the synthesis this stereogenic center is destroyed in the last step by oxidation of the alcohol to a keto group. The further stages in the preparation of **4** are the cleavage of the protecting group at the tertiary alcohol in **13** with sodium in liquid ammonia[13] at $-78\,^{\circ}C$, the acetalisation of the resulting diol **14** with anisaldehydedimethylacetal and *p*-toluenesulfonic acid (PTSA)[14] to give **15**, the desilylation of the protected primary alcohol with tetrabutylammonium fluoride to afford the alcohol **16** and finally the transformation into the iodide **17** according to the Appel procedure[15] with a total yield of 70%. The reaction to **15** could also be performed with *p*-methoxybenzyl methyl ether and dichlorodicyanobenzoquinone (DDQ) in 78% yield. In the deprotection step of **13** a reversed addition technique must be used as a result of the low solubility of the substrate. Thus, a solution of **13** in tetrahydrofuran was slowly added over 30–60 min to a solution of sodium in liquid ammonia to give **14** in 95% yield; with the usual technique the diol **14** was obtained in less than 20% yield even after several hours of reaction time.

For the introduction of the furan unit a cyanohydrin derivative of furan-3-carbaldehyde was used as nucleophile (Umpolung) to react with the iodide **17**. The Umpolung of the aldehyde was performed according to the method of Hünig[16] with trimethylsilyl cyanide in the presence of a catalytic amount of zinc iodide and subsequent deprotonation with



Scheme 2. Total synthesis of (+)-hydroxymyoporone (**4**). a) cat. TfOH, $-78\,^{\circ}C$, CH_2Cl_2, 5 h; b) O_3, CH_2Cl_2, MeOH (5:1), $-78\,^{\circ}C$; PPh_3, $20\,^{\circ}C$; c) *i*BuMgCl, Et_2O, $-78\,^{\circ}C$, 4 h; d) Na, NH_3, $-78\,^{\circ}C$, 30 min; e) anisaldehydedimethylacetal, PTSA, CH_2Cl_2, $20\,^{\circ}C$, 1 h; f) TBAF, THF, $20\,^{\circ}C$, 5 h; g) I_2, PPh_3, imidazole, Et_2O, CH_3CN, $20\,^{\circ}C$, 12 h; h) 2-furanyl-2-trimethylsiloxyacetonitrile, MeLi, THF, $-78\,^{\circ}C$; **17**, 3 h; TBAF, $20\,^{\circ}C$, 30 min; i) 1) $NaBH_4$, EtOH, $20\,^{\circ}C$, 18 h; 2) PPTS, MeOH, $20\,^{\circ}C$, 2 d; j) TPAP, NMO, CH_2Cl_2, $20\,^{\circ}C$, 30 min.

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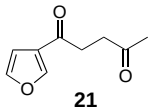
methyllithium. The resulting primary alkylated cyanohydrin was not isolated, but treated directly with tetrabutylammonium fluoride with removal of cyanide to give the ketone **18** in a total yield of 75%. The following cleavage of the acetal resulted in some unexpected problems. Thus, the use of oxidating reagents such as cerium ammonium nitrate (CAN) or DDQ always led to a decomposition of the substrate **18**. A reductive removal of the acetal by catalytic hydrogenation was also unsuccessful. The cleavage could be accomplished under acidic conditions with pyridinium *p*-toluene sulfonate (PPTS) in methanol; however, this was immediately followed by an intramolecular acetalization of the resulting diol with the keto group to give acetal **19**. This compound is rather stable and cannot be transformed into hydroxymyoporone **4** without decomposition. Therefore, first the keto group in **18** was reduced with sodium boranate in ethanol and subsequently the acetal was cleaved with PPTS in methanol to give the triol **20** in 79% yield. The final oxidation of **20** to afford (+)-hydroxymyoporone (**4**) was performed with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine-*N*-oxide (NMO)[17] in quantitative yield. The use of the Dess–Martin-periodinane[18] was unsuccessful and led to a decomposition of the substrate **20**. In addition to the synthesis described, we tried to perform the allylation of substrates which already contain the furan moiety. However, the reaction of **21** and **22** ,[19] respectively, with allylsilane **6** in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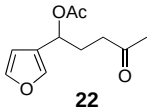
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the presence of **7** and catalytic amounts of TfOH did not lead to the desired compounds but to a reaction mixture which was not further investigated. The failure using **21** is probably a result of the low chemoselectivity of the transformation of the two carbonyl groups and a reaction of the second carbonyl group with an intermediately formed carbocation; **22** was unstable under the acidic reaction conditions.

The synthesized hydroxymyoporone (**4**) with the *R*-configuration at the stereogenic center has an optical rotation of $[\alpha]_D^{20} = +1.3$ ($c = 1.5$ in $CHCl_3$). However, the value for hydroxymyoporone from *Athanasia grandiceps* reported in the literature is $[\alpha]_D^{20} = -0.7$ ($c = 2.7$ in $CHCl_3$)[20] and $[\alpha]_D^{20} = -1.0$ ($c = 2.0$ in $CHCl_3$).[21] Hence it follows that the (−)-hydroxymyoporone isolated from *Athanasia grandiceps* has the *S*-configuration and must be depicted as *ent*-**4**.[20] All other reported spectroscopic data for *ent*-**4** are in agreement with our data. A possible reason for the incorrect configurational assignment in the literature is the fact that the structural proof was made by a synthesis from the sesquiterpenes ipomearon and eremoacetal; however, the absolute configurations of both natural products were unclear at that time.

Conclusion

The presented synthesis of the stress factor hydroxymyoporone (**4**) with a total yield of 37% over all steps, in which the highly selective asymmetric allylation of the ketone **10** is the key step to give the enantiopure homoallylic ether **11a**, is not only the first total synthesis of this natural product, but furthermore leads to a correction of the assignment of the absolute configuration of this substance. In addition, the synthesis clearly shows the strength of the reaction procedure for the stereoselective allylation of ketones, being developed in our group.

Experimental Section

General techniques: All reactions were performed in oven-dried glassware in a nitrogen atmosphere unless otherwise noted. Melting points are determined on a Mettler FP61 and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 digital polarimeter in a 1 dm cell. IR spectra were recorded on a Bruker IFS 25 FT-IR instrument, and ^1H and ^{13}C NMR spectra with a Bruker AM-300 and a Varian VXR-200. Chemical shifts were reported on the δ scale relative to $CDCl_3$ as an internal standard. Mass spectra were measured at 70 eV with a Varian MAT 311A. TLC was performed on precoated silica gel SIL G/UV$_{254}$ plates, and silica gel 32–63 (0.032–0.064 mm) (both Macherey Nagel) was used for column chromatography. Microanalyses were carried out by the Mikroanalytisches Labor des Instituts für Organische Chemie der Universität Göttingen.

(3*S*,1′*S*,2′*S*)-1-*tert*-Butyldiphenylsiloxy-3-methyl-3-(1′-phenyl-2′-trifluoroacetamido-1′-propoxy)-hex-5-en (11a): TfOH (18 μL, 0.20 mmol) was slowly added at −78 °C to a solution of **7** (319 mg, 1.00 mmol), **10** (653 mg, 2.00 mmol), and **6** (228 mg, 2.00 mmol) in CH_2Cl_2 (4 mL). After 5 h of stirring the reaction mixture was quenched by the addition of NEt_3 (0.2 mL) at −78 °C; water (50 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, evaporated, and purified on silica gel (PE/Et_2O 5:1). The homoallylic ether **11a** (586 mg, 0.980 mmol, 98%) was obtained as a colorless oil. The diastereoselectivity was >97.5:2.5. $R_f = 0.45$ (PE/Et_2O 5:1); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.96$ (s, 3H, 3-CH_3), 1.01 (s, 9H, *t*Bu), 1.12 (d, $J = 7.0$ Hz, 3H, 3′-H), 1.71 (t, $J = 7.0$ Hz, 2H, 2-H), 2.27 (dd, $J = 7.0$, 7.0 Hz, 2H, 4-H), 3.58–3.78 (m, 2H, 1-H), 3.92–4.12 (m, 1H, 2′-H), 4.52 (d, $J = 4.5$ Hz, 1H, 1′-H), 5.03 (d, $J = 18.0$ Hz, 1H, 6-H_a), 5.06 (d, $J = 10.0$ Hz, 1H, 6-H_b), 5.76 (ddd, $J = 18.0$, 10.0, 7.0 Hz, 1H, 5-H), 6.32 (br d, $J = 8.0$ Hz, 1H, N-H), 7.11–7.66 (m, 15H, Ph-H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 16.77$ (C-3′), 19.06 (*t*Bu-CH_3), 23.83 (3-CH_3), 26.81 (*t*Bu-C), 42.06 (C-2), 44.10 (C-4), 51.74 (C-2′), 60.12 (C-1), 74.19 (C-1′), 78.11 (C-3), 115.81 (q, $^1J_{C,F} = 288$ Hz, CF_3), 118.06 (C-6), 126.55, 127.61, 127.69, 127.75 (Ph-C), 134.00 (C-5), 135.52, 141.13 (Ph-C), 156.37 (q, $^2J_{C,F} = 37$ Hz, C=O).

(3*R*,1′*S*,2′*S*)-5-*tert*-Butyldiphenylsiloxy-3-methyl-3-(1′-phenyl-2′-trifluoroacetamido-1′-propoxy)-1-pentanal (12): Ozone was bubbled through a solution of the alkene **11a** (1.43 g, 2.39 mmol) in a mixture of CH_2Cl_2 (50 mL) and MeOH (10 mL) at −78 °C until a blue color remained permanent. The solution was saturated with nitrogen and PPh_3 (885 mg, 3.38 mmol) was added. The mixture was stirred for 30 min at −78 °C and then allowed to warm to room temperature. The solvent was evaporated and the residue purified on silica gel to give the aldehyde **12** (1.36 g, 2.27 mmol, 95%) as a colorless oil. $R_f = 0.24$ (PE/Et_2O 2:1); $[\alpha]_D^{20} = +23.3$ ($c = 1$, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.00$ (s, 9H, *t*Bu-CH_3), 1.09 (d, $J = 7.0$ Hz, 3H, 3′-H), 1.21 (s, 3H, 3-CH_3), 1.77 (dd, $J = 6.5$, 6.5 Hz, 2H, 4-H), 2.68 (d, $J = 2.5$ Hz, 2H, 2-H), 3.51–3.74 (m, 2H, 5-H), 3.98–4.26 (m, 1H, 2′-H), 4.56 (d, $J = 4.5$ Hz, 1H, 1′-H), 6.38 (br d, $J = 8.0$ Hz, 1H, N-H), 7.10–7.62 (m, 15H, Ph-H), 9.82 (dd, $J = 2.5$, 2.5 Hz, 1H, 1-H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 16.17$ (C-3′), 18.98 (*t*Bu-CH_3), 24.38 (3-CH_3), 26.75 (*t*Bu-C), 42.34 (C-4), 51.34 (C-2′), 52.57 (C-2), 59.88 (C-5), 65.81 (C-3), 74.64 (C-1′), 115.54 (q, $^1J_{C,F} = 289$ Hz, CF_3), 126.70, 127.68, 128.38, 129.72, 135.46, 140.13 (Ph-C), 156.85 (q, $^2J_{C,F} = 37$ Hz, C=O), 201.76 (C-1); MS (70 eV, FD): *m/z* (%): 542 (6) $[M - t\text{Bu}]^+$, 353 (11) $[M - C_{11}H_{11}F_3NO_2]^+$, 269 (53) $[TBDPSOCH_2]^+$, 230 (100) $[C_{11}H_{11}F_3NO]^+$; $C_{33}H_{40}F_3NO_4Si$: calcd C 66.09, H 6.72; found C 66.01, H 6.83.

(3*R*,5*RS*,1′*S*,2′*S*)-1-*tert*-Butyldiphenylsiloxy-3,7-dimethyl-3-(1′-phenyl-2′-trifluoroacetamido-1′-propoxy)-5-octanol (13): A solution of isobutylmagnesium chloride (167 μL of a 2 M solution in THF, 333 μmol) was added at

$-78\,^{\circ}C$ to a solution of the aldehyde **12** (100 mg, 167 μmol) in Et_2O (15 mL). The mixture was stirred for 1 h at this temperature, then allowed to warm to room temperature and stirred for further 3 h. Water (50 mL) was added, the aqueous phase extracted with Et_2O (3×50 mL), the combined organic phases dried over Na_2SO_4, and the solvent evaporated. The residue was purified on silica gel (PE/Et_2O 3:2) and the alcohol **13** (105 mg, 160 μmol, 96%) was isolated as a colorless oil (1:1 mixture of diastereomers). $R_f = 0.51$ (PE/Et_2O 1:1); $[\alpha]_D^{20} = -22.4$ ($c = 1$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.87$ (d, $J = 6.5$ Hz, 3H, 3′-H), 0.94/0.97 (s, 9H, *t*Bu-CH_3), 1.07 (d, $J = 7.0$ Hz, 3H, 7-CH_3), 1.10 (d, $J = 7.0$ Hz, 3H, 8-H), 1.15–1.95 (m, 7H, 2-H, 4-H, 6-H, 7-H), 1.42 (s, 3H, 3-CH_3), 3.31–3.59 (m, 3H, 1-H, 5-H), 3.83–4.11 (m, 1H, 2′-H), 4.53–4.73 (m, 1H, 1′-H), 6.52/6.62 (d, $J = 8.0$ Hz, 1H, NH), 7.10–7.64 (m, 15H, Ph-H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 15.11/15.34$ (C-3′), 18.94 (*t*Bu-CH_3), 22.04/22.19 (C-8), 23.22/23.34 (7-CH_3), 24.27/24.34 (3-CH_3), 25.07 (C-7), 26.72/26.76 (*t*Bu-C), 41.06/43.07 (C-4), 46.16/47.42 (C-2), 47.50/47.77 (C-6), 51.36/51.42 (C-2′), 60.05/60.37 (C-1), 66.39 (C-5), 74.30/74.67 (C-1′), 79.92/80.51 (C-3), 115.13 (q, $^1J_{C,F} = 288$ Hz, CF_3), 126.90, 127.57/127.62, 128.28/128.37, 129.58/129.64, 135.44, 139.78/140.40 (Ph-C), 156.60 (q, $^2J_{C,F} = 37$ Hz, C=O); MS (70 eV, CI (NH_3)): *m/z* (%): 675 (100) $[M + NH_4]^+$; $C_{37}H_{50}F_3NO_4Si$: calcd C 67.55, H 7.66; found C 67.37, H 7.49.

(3*R*,5*RS*)-1-*tert*-Butyldiphenylsiloxy-3,7-dimethyl-3,5-octanediol (14): A solution of the benzyl ether **13** (1.00 g, 1.52 mmol) in THF (15 mL) was slowly (0.5 mL per min) added at $-78\,^{\circ}C$ to a solution of Na (175 mg, 7.60 mmol) in liquid NH_3 (150 mL). The solution was stirred for 30 min at this temperature, and afterwards solid NH_4Cl was added until the color of the solution turned to yellow. The ammonia was evaporated at room temperature, and water (100 mL) poured to the residue. The aqueous phase was extracted with Et_2O (3×100 mL), the combined organic layers were dried over Na_2SO_4, and the solvent was evaporated. The residue was purified on silica gel to give the alcohol **14** (617 mg, 1.44 mmol, 95%) as a colorless oil (1:1 mixture of diastereomers). $R_f = 0.37/0.41$ (PE/Et_2O 1:1); $[\alpha]_D^{20} = -22.3$ ($c = 1$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.86$–1.02 (m, 6H, 8-H, 7-CH_3), 1.05 (s, 9H, *t*Bu-CH_3), 1.08–1.85 (m, 6H, 2-H, 4-H, 6-H), 1.44 (s, 3H, 3-CH_3), 2.15–2.39 (m, 1H, 7-H), 3.78–4.03 (m, 2H, 1-H), 4.03–4.22 (m, 1H, 5-H), 4.27 (br s, 1H, OH), 4.48 (br s, 1H, OH), 7.35–7.74 (m, 10H, Ph-H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 18.92/19.62$ (*t*Bu-CH_3), 22.36/22.42 (C-8), 23.23/23.28 (7-CH_3), 24.27 (3-CH_3), 26.74/27.01 (*t*Bu-C), 28.21/28.45 (C-7), 39.46/41.75 (C-4), 43.52/43.86 (C-2), 48.46/48.53 (C-6), 61.45/ 61.69 (C-1), 66.44/66.65 (C-5), 74.27/74.33 (C-3), 127.84, 128.60, 129.30, 129.96, 134.55, 135.50 (Ph-C); MS (70 eV, FD): *m/z* (%): 428 (3) $[M]^+$, 267 (17) $[TBDPSOC]^+$, 199 (100) $[Ph_2SiOH]^+$, 69 (19) $[C_5H_9]^+$; $C_{26}H_{40}O_3Si$: calcd C 72.85, H 9.40; found C 72.67, H 9.37.

(3*R*,5*RS*)-1-*tert*-Butyldiphenylsiloxy-3,7-dimethyl-3,5-octanediol-*p*-methoxybenzylidenacetal (15): *p*-Toluenesulfonic acid (cat.) was added at room temperature to a solution of the diol **14** (100 mg, 233 μmol) and anisaldehydedimethylacetal (64.0 mg, 350 μmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 1 h, NEt_3 (five drops) was added and the solvent was evaporated. The residue was purified on silica gel (PE/Et_2O 6:1) and the acetal **15** (201 mg, 201 μmol, 86%) was obtained as a colorless oil (1.2:1 mixture of diastereomers). $R_f = 0.34$ (PE/Et_2O 4:1); $[\alpha]_D^{20} = +12.0^{\circ}$ ($c = 1$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.71$–1.05 (m, 6H, 8-H, 7-CH_3), 1.06 (s, 9H, *t*Bu-CH_3), 1.10–1.71 (m, 4H, 2-H, 6-H), 1.21 (s, 3H, 3-CH_3), 1.74–2.21 (m, 2H, 4-H), 2.22–2.46 (m, 1H, 7-H), 3.60–4.06 (m, 3H, 1-H, 5H), 3.74 (s, 3H, OCH_3), 5.36 (s, 1H, 1′-H), 6.76–6.95 (m, 2H, Ph-H), 7.19–7.49 (m, 8H, Ph-H), 7.55–7.74 (m, 4H, Ph-H); ^{13}C NMR (50 MHz, $CDCl_3$, main isomer): $\delta = 19.10$ (*t*Bu-CH_3), 22.43 (C-8), 23.22 (7-CH_3), 24.03 (3-CH_3), 26.89 (*t*Bu-C), 29.01 (C-7), 36.76 (C-4), 42.06 (C-2), 45.10 (C-6), 55.27 (OCH_3), 59.88 (C-1), 70.84 (C-5), 73.28 (C-3), 94.35 (C-1′), 113.41, 127.26, 127.65, 127.87, 135.53, 159.53 (Ph-C); MS (70 eV, FD): *m/z* (%): 546 (6) $[M]^+$, 489 (6) $[M - t\text{Bu}]^+$, 337 (24) $[TBDPSOC_6H_{10}]^+$, 269 (28) $[TBDPSOCH_2]^+$, 137 (100) $[C_8H_9O_2]^+$; $C_{34}H_{46}O_4Si$: calcd C 74.68, H 8.48; found C 74.70, H 8.31.

(3*R*,5*RS*)-3,7-Dimethyl-1,3,5-octanetriol-3,5-*p*-methoxybenzylidenacetal (16): A solution of the silyl ether **15** (220 mg, 402 μmol) and tetrabutylammonium fluoride (634 mg, 2.01 mmol, TBAF · $3H_2O$) in THF (10 mL) was stirred at room temperature for 5 h. The solvent was evaporated and the residue purified on silica gel (PE/Et_2O 1:3). The alcohol **16** (123 mg, 399 μmol, 99%) was isolated as a colorless oil (1.2:1 mixture of diastereomers). $R_f = 0.27$ (PE/Et_2O 1:2); $[\alpha]_D^{20} = +20.5$ ($c = 1$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.73$–1.04 (m, 6H, 8-H, 7-CH_3), 1.11–1.95 (m, 5H, 2-H, 6-H, OH), 1.33 (s, 3H, 3-CH_3), 1.96–2.24 (m, 1H, 7-H), 2.24–2.75 (m, 2H, 4-H), 3.60–4.16 (m, 3H, 1-H, 5-H), 3.77 (s, 3H, OCH_3), 5.76 (s, 1H, 1′-H), 6.86 (d, $J = 8.5$ Hz, 2H, Ph-H), 7.39 (d, $J = 8.5$ Hz, 2H, Ph-H); ^{13}C NMR (50 MHz, $CDCl_3$, main isomer): $\delta = 22.43$ (C-8), 23.05 (7-CH_3), 23.95 (3-CH_3), 28.51 (C-7), 35.61 (C-4), 42.38 (C-2), 45.03 (C-6), 55.26 (OCH_3), 59.12 (C-1), 70.93 (C-5), 74.37 (C-3), 94.93 (C-1′), 113.60, 127.39, 129.55, 159.76 (Ph-C); MS (70 eV, FD): *m/z* (%): 308 (33) $[M]^+$, 139 (85) $[C_{10}H_{19}]^+$, 137 (100) $[C_8H_9O_2]^+$, 135 (82) $[C_8H_7O_2]^+$, 81 (37) $[C_5H_5O]^+$; $C_{18}H_{28}O_4$: calcd C 70.10, H 9.15; found C 70.12, H 9.16.

(3*S*,5*RS*)-3,7-Dimethyl-1-iodo-3,5-octanediol-*p*-methoxybenzylidenacetal (17): Iodine (419 mg, 1.66 mmol) was added at $0\,^{\circ}C$ to a solution of the alcohol **16** (255 mg, 827 μmol), imidazole (107 mg, 1.57 mmol), and PPh_3 (390 mg, 1.48 mmol) in a mixture of Et_2O (4.0 mL) and CH_3CN (0.7 mL). The mixture was stirred for 12 h under exclusion of light and then adsorbed on silica gel. Eluation with PE/Et_2O (7:1) gave the iodide **17** (300 mg, 717 μmol, 87%) as a colorless, light-sensitive oil (1.2:1 mixture of diastereomers). $R_f = 0.47$ (PE/Et_2O 5:1); $[\alpha]_D^{20} = -27.0$ ($c = 1$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.90$ (d, $J = 7.0$ Hz, 3H, 8-H), 0.95 (d, $J = 7.0$ Hz, 3H, 7-CH_3), 1.09–1.70 (m, 4H, 2-H, 6-H), 1.28 (s, 3H, 3-CH_3), 1.78–2.43 (m, 3H, 4-H, 7-H), 3.12–3.40 (m, 2H, 1-H), 3.80 (s, 3H, OCH_3), 3.92–4.09 (m, 1H, 5-H), 5.59 (s, 1H, 1′-H), 6.87 (d, $J = 8.5$ Hz, 2H, Ph-H), 7.41 (d, $J = 8.5$ Hz, 2H, Ph-H); ^{13}C NMR (50 MHz, $CDCl_3$, main isomer): $\delta = -1.79$ (C-1), 22.46 (C-8), 23.15 (7-CH_3), 24.01 (3-CH_3), 27.92 (C-7), 39.96 (C-4), 41.55 (C-2), 45.04 (C-6), 55.30 (OCH_3), 70.86 (C-5), 75.27 (C-3), 94.65 (C-1′), 113.58, 127.26, 131.42, 159.76 (Ph-C); MS (70 eV, FD): *m/z* (%): 418 (10) $[M]^+$, 199 (100) $[C_4H_8IO]^+$, 135 (31) $[C_8H_7O_2]^+$, 69 (17) $[C_5H_9]^+$; $C_{18}H_{27}IO_3$: calcd 418.1004; found 418.1004 (HRMS).

(4*S*,6*RS*)-4,8-Dimethyl-1-furan-3′-ylnonane-1-on-4,6-diol-*p*-methoxybenzylidenacetal (18): A solution of MeLi in Et_2O (376 μL of a 1.6 M solution, 602 μmol) was added at $-78\,^{\circ}C$ to a solution of the cyanohydrin (134 mg, 688 μmol) in THF (7 mL). After stirring for 30 min at this temperature the iodide **17** (72.0 mg, 172 μmol), dissolved in Et_2O (0.3 mL), was added. The mixture was stirred at $-78\,^{\circ}C$ for 30 min, allowed to warm to room temperature within 3 h and tetrabutylammonium fluoride (134 mg, 516 μmol, TBAF · $3H_2O$) was added. After the reaction mixture was stirred for a further 30 min, the solvent was evaporated and the residue purified on silica gel. The ketone **18** (50 mg, 129 μmol, 75%) was isolated as a colorless oil (1.2:1 mixture of diastereomers). $R_f = 0.27$ (PE/Et_2O 4:1); $[\alpha]_D^{20} = -5.0$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.90$ (d, $J = 7.0$ Hz, 3H, 9-H), 0.94 (d, $J = 7.0$ Hz, 3H, 8-CH_3), 1.30 (s, 3H, 4-CH_3), 1.48–2.08 (m, 5H, 3-H, 7-H, 8-H), 2.40–2.88 (m, 2H, 5-H), 2.77–3.02 (m, 2H, 2-H), 3.80 (s, 3H, OCH_3), 3.94–4.19 (m, 1H, 6-H), 5.57 (s, 1H, 1″-H), 6.77 (d, $J = 2.0$ Hz, 1H, 4′-H), 6.87 (d, $J = 8.5$ Hz, 2H, Ph-H), 7.31–7.52 (m, 3H, Ph-H, 5′-H), 8.03 (s, 1H, 2′-H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 22.38$ (C-9), 23.05 (8-CH_3), 23.91 (4-CH_3), 27.63 (C-7), 28.38 (C-8), 34.01 (C-3), 42.09 (C-5), 45.07 (C-2), 55.21 (OCH_3), 70.82 (C-6), 73.29 (C-4), 94.58 (C-1″), 108.51 (C-4′), 113.52, 127.27 (Ph-C), 127.59 (C-3′), 131.67 (Ph-C), 144.15 (C-5′), 146.99 (C-2′), 159.66 (Ph-C), 194.76 (C-1); MS (70 eV, FD): *m/z* (%): 386 (4) $[M]^+$, 234 (33) $[M - PMB]^+$, 135 (100) $[MePhCO]^+$, 95 (43) [furanoyl]$^+$, 41 (54) $[C_3H_5]^+$; $C_{23}H_{30}O_5$: calcd 386.2093; found 386.2093 (HRMS).

(4*R*)-(+)-Hydroxymyoporone (4): $NaBH_4$ (1.80 mg, 46.6 μmol) was added at room temperature to a solution of the ketone **18** (18.0 mg, 46.6 μmol) in EtOH (5 mL). After the solution was stirred for 30 min, further $NaBH_4$ (1.80 mg, 46.6 μmol) was added. The reaction mixture was stirred for a further 18 h. Afterwards the solvent was evaporated and the residue filtered through a small pad of silica gel. The crude product was dissolved in MeOH (5 mL), PPTS (cat.) added, and the mixture stirred for 2 d. K_2CO_3 (6.50 mg, 93.2 μmol) was added to the solution and the solvent was evaporated. The residue was dissolved in Et_2O and filtered through a small pad of silica gel to give the crude triol **20** (10.0 mg, 37.0 μmol) as a colorless oil. Tetrapropylammonium perruthenate (2.40 mg, 6.70 μmol) was added at room temperature to a mixture of **20** (18.0 mg, 66.6 μmol), molecular sieves 4 Å (67 mg), and *N*-methylmorpholine-*N*-oxide (24 mg, 201 mmol) in CH_2Cl_2 (0.30 mL). After stirring for 30 min, the solution was filtered through silica gel (Et_2O) and (+)-hydroxymyoporone (**4**) (17.7 mg, 66.6 μmol, 79%) was obtained as a colorless oil after column chromatography. $R_f = 0.23$ (PE/Et_2O 1:1); $[\alpha]_D^{20} = +1.3$ ($c = 1.5$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.93$ (d, $J = 7.0$ Hz, 6H, 9-H, 8-CH_3), 1.23 (s, 3H, 4-CH_3), 1.83 (ddd, $J = 14.5$, 9.0, 6.0 Hz, 1H, 3-H_a), 1.96 (ddd, $J = 14.5$, 9.0, 6.0 Hz, 1H, 3-H_b), 2.15 (dsept, $J = 7.0$, 7.0 Hz, 1H, 8-H), 2.30 (d, $J = 7.0$ Hz, 2H, 7-H), 2.60 (s, 2H, 5-H), 2.86 (ddd, $J = 16.0$, 9.0, 6.0 Hz, 1H, 2-H_a) 2.96

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(ddd, $J = 16.0, 9.0, 6.0$ Hz, 1H, 2-H_b), 3.32 (s, 1H, OH), 6.77 (d, $J = 2.0$ Hz, 1H, 4′-H), 7.44 (dd, $J = 2.0, 2.0$ Hz, 1H, 5′-H), 8.08 (d, $J = 2.0$ Hz, 1H, 2′-H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 22.45$ (C-9), 22.50 (8-CH_3), 24.39 (4-CH_3), 26.63 (C-8), 34.67 (C-3), 35.31 (C-2), 52.20 (C-7), 53.56 (C-5), 70.97 (C-4), 108.56 (C-4′), 127.47 (C-3′), 144.12 (C-5′), 147.23 (C-2′), 195.08 (C-1), 213.27 (C-6); MS (70 eV, FD): *m/z* (%): 266 (3) $[M]^+$, 167 (37) $[M - C_6H_{11}O]^+$, 95 (100) $[C_5H_3O_2]^+$, 85 (51) $[C_5H_9O]^+$, 57 (40) $[C_4H_9]^+$, 43 (36) $[C_2H_3O]^+$; $C_{15}H_{22}O_4$: calcd 266.1518; found 266.1518 (HRMS).

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