Formal Total Synthesis of Salvinorin A

Marc Halang and Martin E. Maier*[a]

The generation of the quaternary stereocenter at the C9 position of salvinorin A precursors by the Claisen rearrangement was investigated. The required allyl alcohol was prepared from a Wieland-Miescher ketone using a known γ-hydroxylation, reduction of the enone double bond, cyanohydrin formation, and elimination, yielding an unsaturated nitrile. A two-step reduction led to the required allyl alcohol. The subsequent Johnson-Claisen rearrangement provided a mixture of two diastereomeric 1,4-unsaturated esters in a ratio of around 2.6:1. The major isomer could be converted to a key intermediate of the Hagiwara synthesis of salvinorin A.

Introduction

Among the family of clerodane diterpenes, salvinorin A (**1**) clearly stands out (Figure 1). This has to do with the fact that it is a potent natural hallucinogen. This came as a surprise since it is not an alkaloid. Its isolation from leaves of *Salvia divinorum* and its structure were reported in 1982.[1] This plant is used by indigenous people in Mexico for ritual purposes. The discovery that salvinorin A (**1**) is a potent and selective K opioid receptor agonist[2] triggered a lot of interest among the biology and chemistry communities. Accordingly, a SciFinder search on salvinorin A generates around 500 hits. Continuing efforts led to the isolation of around 20 salvinorin A analogs from *Salvia divinorum*.[3]

Some related diterpenes, such as 8-epidiosbulbin E acetate (**2**) from *Dioscorea bulbifera* L. (Figure 1), have also been isolated.[4] It was reported that **2** has plasmid-curing activity against multidrug-resistant bacteria by rendering them sensitive to antibiotics again. Collybolide (**3**) was isolated from the mushroom *Collybia maculata*. Even though the furan ring in collybolide (**3**) points to the α-face of the molecule, it was reported that it is also an agonist for K opioid receptors with an activity comparable to **1**.[5]

In general, agonists of opioid receptors show analgesic effects but are typically also associated with side effects. Agonists for the kappa opioid receptor (KOR) hold promise for the treatment of Central Nervous System (CNS) disorders. A recent review article summarizes the effects of structural modifications, mostly on the periphery of the core structure, on the biological activity.[6] For example, replacement of the acetate group at C2 by alkoxymethyl ethers can lead to analogs with smaller K_i values. Modifications at C4 are generally detrimental. Small changes on the furan ring seem to be tolerated. Synthetic routes that allow for serious modifications on the core structure have been published by Shenvi et al.[7] and Prisinzano et al.[8]

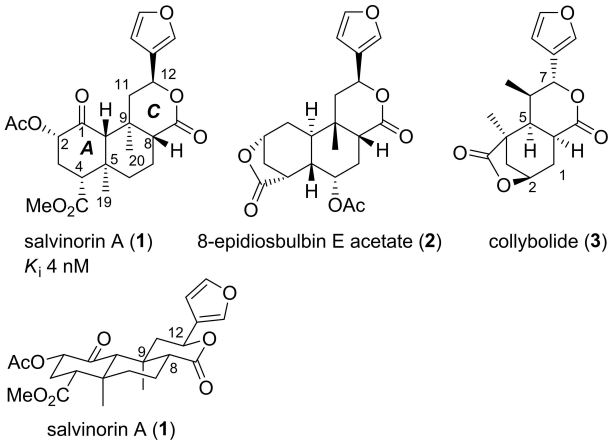

Figure 1. Structure of salvinorin A (**1**), including an alternative depiction showcasing the spatial substituent arrangement (bottom), and some related compounds.

Even though many routes to clerodane diterpenes are known,[9] the structure of salvinorin A (**1**) presents special challenges. These include seven stereocenters, the C ring lactone with a 3-furyl substituent and the two axial methyl groups a C5 and C9. As has been pointed out by Shenvi et al.,[7] the 1,3-diaxial interaction between 9-Me and 12-H facilities epimerization at C8, leading to loss in activity.

So far, six total syntheses for salvinorin A (**1**) were reported by four groups. Key issues are the synthesis of the decalin core and the time of the furan installation (Scheme 1).[10] In the Evans synthesis, the furan was introduced early on into the macrolactone **4** which could be cyclized to decalin **5** through a domino Michael reaction.[11] The Hagiwara group developed two routes to **1** from Wieland-Miescher ketone derivative **6**.[12] In a key step, the quaternary center at C9 was created by an enolate alkylation. The problem in this step is the unwanted elimination of the hydroxyl group from the intermediate

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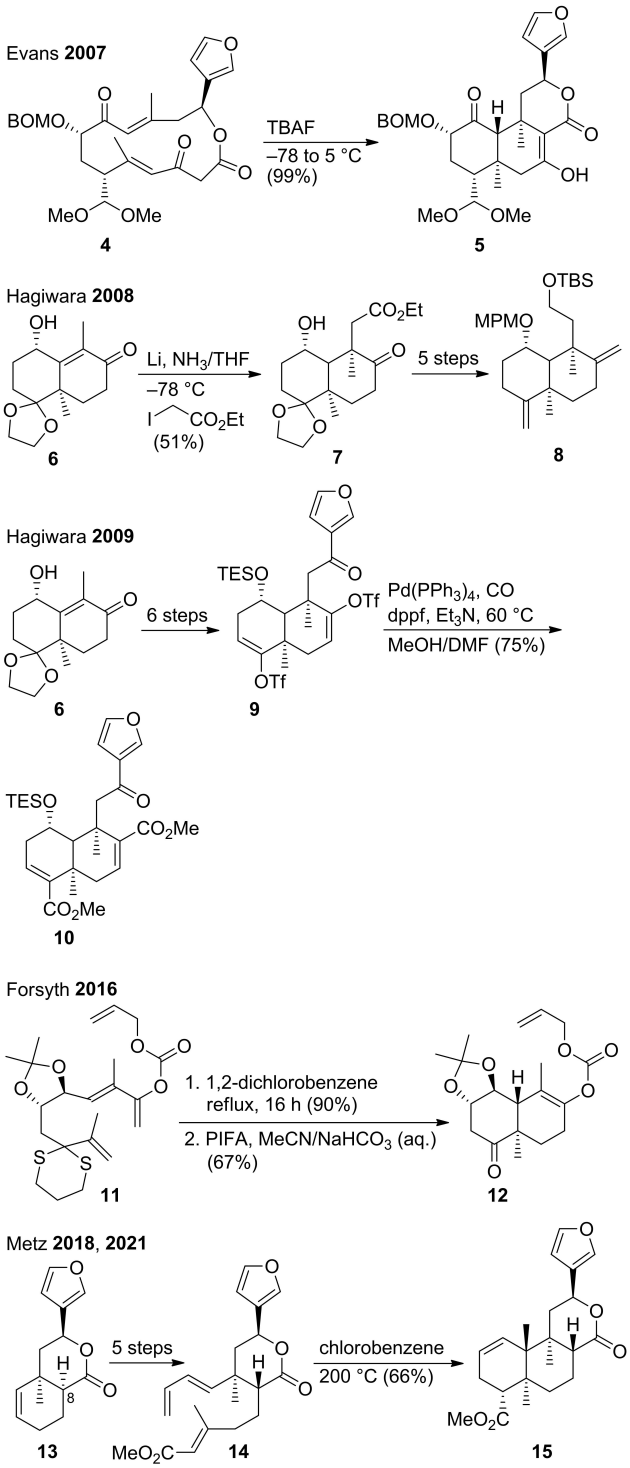
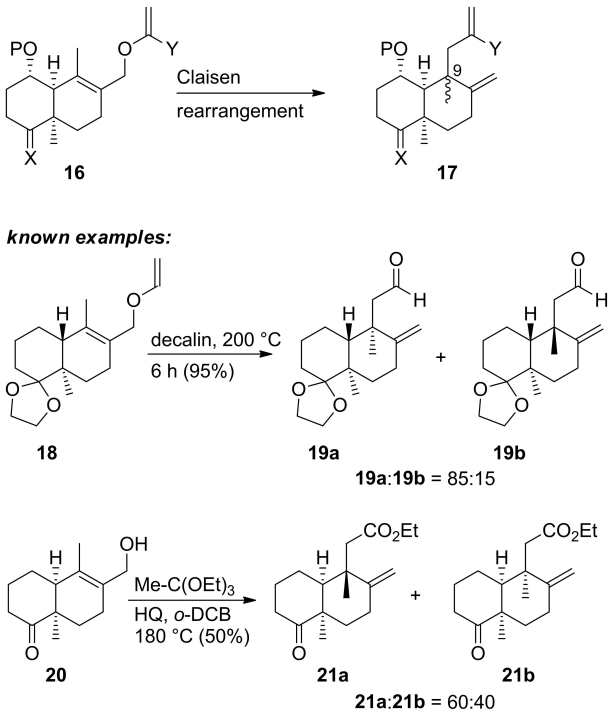


Scheme 1. Key steps in previous syntheses of salvinorin A (**1**). TES = triethylsilyl, BOM = benzyloxymethyl, MPM = (4-methoxyphenyl)methyl (*para*-methoxybenzyl), dppf = 1,1′-bis(diphenylphosphino)ferrocene, PIFA = (bis-(trifluoroacetoxy)iodo)benzene (phenyliodine bis(trifluoroacetate).

enolate. The two routes differ in the way the functional groups at C4 and C8 were introduced. In the first route, hydroboration on the exocyclic double bonds on diene **8** came to use, whereas in the second route, carbonylation on the enol triflates **9** served this purpose. Both routes feature late-stage introduction of the 3-furyl group. A key step in the synthesis of Forsyth et al.[13] was an intramolecular Diels-Alder reaction of triene **11**. This substrate originated from D-tartrate. A Tsuji allylation on enol carbonate **12** set the stereochemistry at C9. The Metz group published two similar routes to salvinorin A (**1**).[14] In a key step, triene **14**, which already contained the C-ring, underwent an intramolecular Diels-Alder reaction to the salvinorin A core **15**. Remarkably, substrate **13** also had been prepared by an intramolecular Diels-Alder reaction.

Results and Discussion

We wondered whether other methods would allow for a concise introduction of the C9 quaternary center on substrates that would be easily available from Wieland-Miescher ketone derivatives. In this context, we envisioned a Claisen rearrangement on compounds of type **16**. Such reactions had previously been performed on less functionalized compounds (Scheme 2). Kakisawa et al. reported the formation of the two enals **19a** and **19b** in a ratio of 85:15 (95% total yield) upon heating allyl vinyl ether **18** to 200 °C.[15] In a related study, Terashima et al. described the Johnson-Claisen rearrangement on *cis*-decalin derivative **20**.[16] This led to the preferential rearrangement on the α-face, giving unsaturated esters **21a** and **21b** (ratio = 3:2, 50% combined yield). In the first example, it was argued that the axial methyl group interferes with the transition state of the rearrangement on the α-face. In the second example, which is described for a *cis*-decalin, it seems that rearrangement is favored *syn* to the allylic C–H. At the outset it was not clear



Scheme 2. Plan for creation of the stereochemistry at C9 (salvinorin A numbering) together with some known related examples from the literature. HQ = hydroquinone, DCB = *ortho*-dichlorobenzene (1,2-dichlorobenzene).

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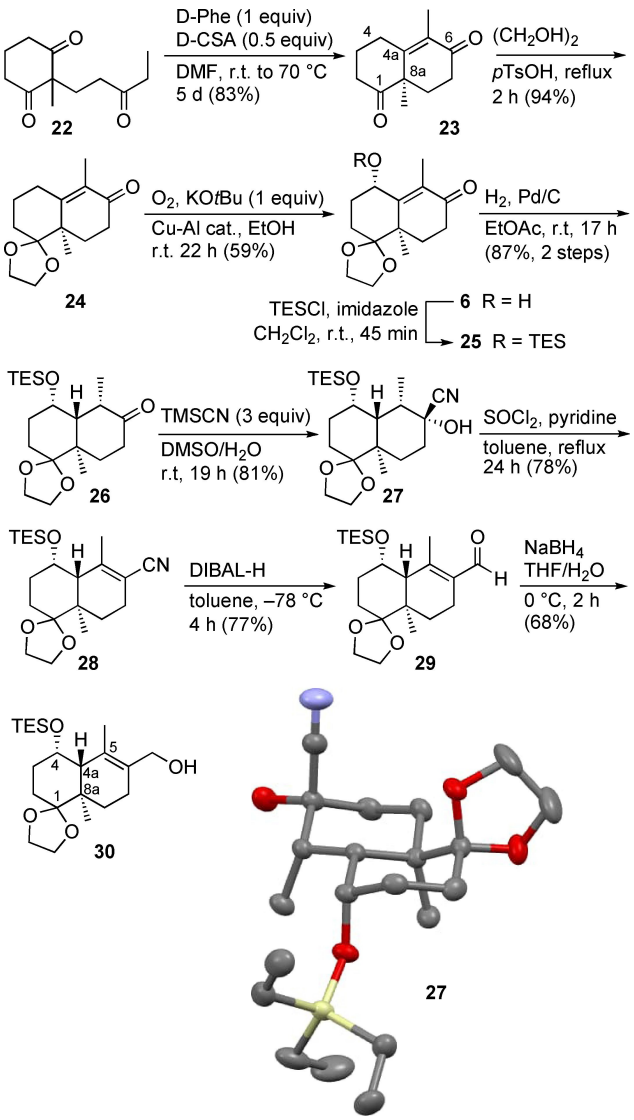
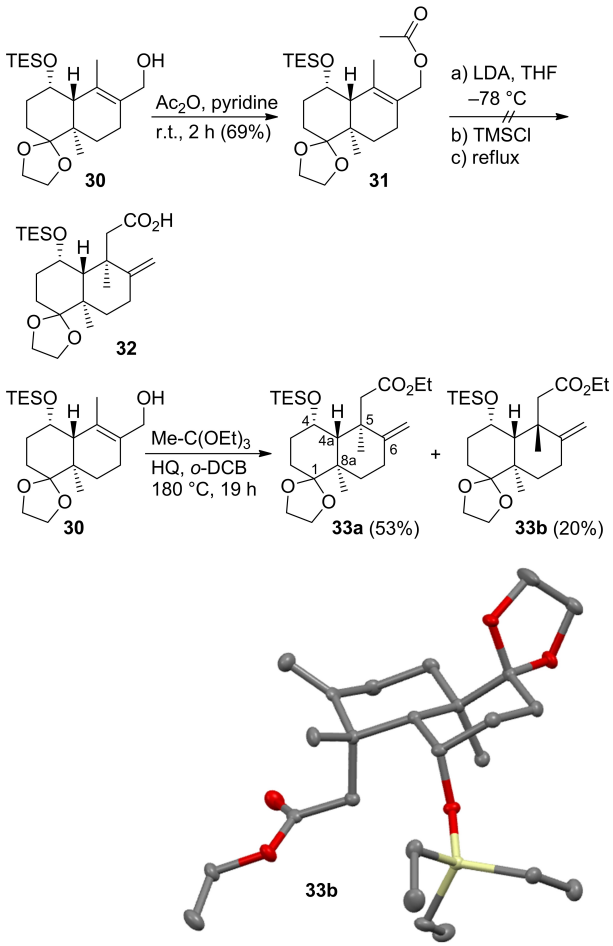
what an influence a hydroxy substituent at C4 (decalinone numbering) would have on the facial selectivity of a Claisen rearrangement of substrates **16**. One might speculate that the axial positioned OP group directs the rearrangement to the β-face by interfering with the rearrangement transition state on the α-face. In this paper, we describe our results of this study.

We started the synthesis of Wieland-Miescher ketone **23** from triketone **22**,[17] using conditions developed by Theodorakis et al. where D-phenylalanine (Phe; 1 equiv.) and D-camphorsulfonic acid (CSA; 0.5 equiv.) served as chirality inducers (Scheme 3).[17,18] Subsequent acetalization of the nonconjugated keto function provided enone **24** in excellent yield as well.[17] Hydroxylation of the γ-position of enone **24** using oxygen in presence of KO*t*Bu and the copper-aluminium mixed oxide (Cu–Al Ox) furnished alcohol **6**.[19] The method used by the Hagiwara group to prepare compound **6** from enone **24** (O_2, KOH, MeOH, 2.7 d, r.t.) was less efficient in our hands.[12a,20] The best yield we could get under these conditions was 47% of **6**. Based on literature precedence, the stereochemistry at C4 was assigned as shown, which means that hydroxylation took place on the α-face.[12a,21] Accordingly, hydrogenation of the enone double bond on the derived silyl ether **25** was expected to occur from the top-face, giving the *trans* decalinone **26** in good yield as a single isomer, which was indeed the case.[22] In order to establish the allyl alcohol functionality, ketone **26** was converted to cyanohydrin **27** with trimethylsilyl cyanide in a DMSO/H_2O mixture.[23] The structure of **27** was unambiguously confirmed by an X-ray analysis. It clearly showed the all-*cis* arrangement of the substituents at C4, C5 and C8a. Treatment of cyanohydrin **27** with thionyl chloride and pyridine led to unsaturated nitrile **28** with the correct double bond position. A two-step reduction of the nitrile, first with DIBAL–H to enal **29**, second with sodium borohydride, gave rise to allyl alcohol **30**. A similar sequence to convert a ketone to an allyl alcohol had been used by Kakisawa et al.[15] in the synthesis of a *trans*-clerodane diterpene.

We first tried the Ireland-Claisen variant[24] on the acetate **31**, easily obtained from alcohol **30** (Scheme 4). Deprotonation of the acetate, followed by enolate trapping with trimethylsilyl



Scheme 3. Synthesis of allyl alcohol **30** as substrate for the Claisen rearrangement. ORTEP plot of cyanohydrin **27** (hydrogen atoms omitted for clarity). Displacement ellipsoids are drawn at the 50% probability level.



Scheme 4. Study on the Claisen rearrangement on allyl alcohol **30**. ORTEP plot of unsaturated ester **33b**. Displacement ellipsoids are drawn at the 50% probability level.

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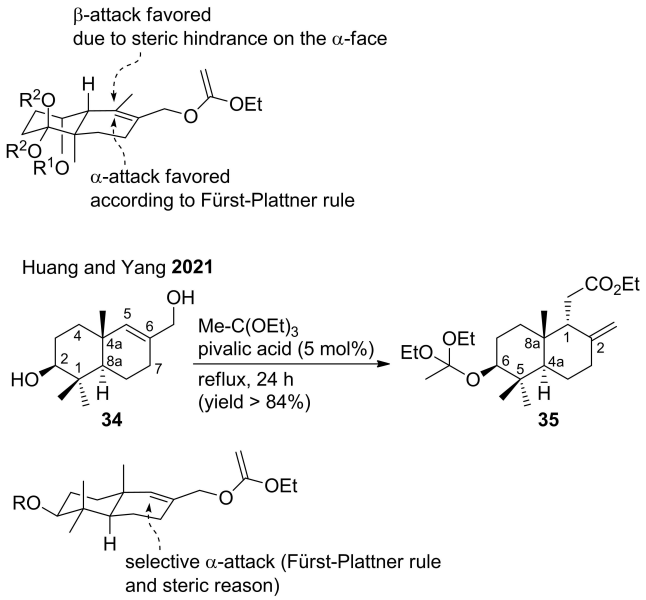
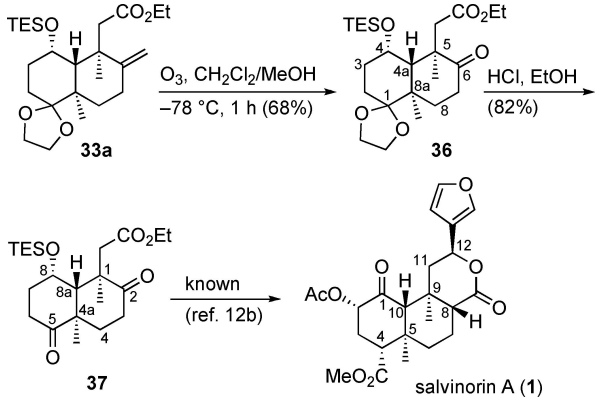
chloride and subsequent heating of the silyl ketene acetal led to a complex mixture, which contained none of the acid **32**. Therefore, we switched to the Johnson-Claisen rearrangement.[25] Thus, stirring allyl alcohol **30** with an excess of triethyl orthoacetate in *ortho*-dichlorobenzene at 180 °C for 18 h led to the rearranged esters **33 a** and **33 b**. The conditions for the rearrangement were those reported by Terashima et al.[16] The desired isomer **33 a** was obtained in 53% yield. The minor diastereomer **33 b** was formed in around 20% yield. Major differences in the ^{13}C NMR spectra of the two isomers are the different chemical shift values for the C4a carbon atoms. In **33 a**, C4a resonates at $\delta = 46.5$ ppm, whereas the corresponding resonance in **33 b** appears at $\delta = 54.2$ ppm. Separation of the isomers was possible by flash chromatography on silica gel. The structure of the minor isomer **33 b** could be confirmed by X-ray analysis (Scheme 4).



Scheme 5. Model to explain the observed diastereoselectivity on decalin systems having an allyl alcohol in the substrate. The Fürst-Plattner rule and steric effects may counteract each other or act synergistically as in the rearrangement of **34** to **35**.



Scheme 6. Conversion of 1,4-unsaturated ester **33 a** to the known salvinorin A intermediate **37**.

One might speculate that the moderate selectivity results from two effects counteracting each other (Scheme 5). Thus, attack on the α-face would be favored due to a Fürst-Plattner type situation, since the transition state would have a chair-like conformation. However, since the α-face is sterically hindered due to the axial methyl and the $OSiEt_3$ group, the β-attack, overall, seems to be favored. In a recent example from the literature, both the stereoelectronic effect (Fürst-Plattner rule) and steric effects seem to act synergistically. Thus, the Johnson-Claisen rearrangement on allyl alcohol **34** gave only the desired α-isomer **35** (Scheme 5).[16b] We believe that this simple model might help to predict or to rationalize the diastereoselectivity of a Claisen rearrangement on related substrates.

For chemical correlation, acetic ester derivative **33 a** was converted to known[12b] **37** in two steps (Scheme 6). Thus, our work constitutes a formal total synthesis of salvinorin A (**1**). We note that the modern catalysts used for enantioselective Robinson annulation do tolerate a range of substituents on the substrates. Thus, this strategy might be used to make salvinorin A analogs with different alkyl groups at C10, C5 or C9.

Conclusion

Wieland-Miescher ketone **23** was converted in 12 steps to the known diketo ester **37**, a key intermediate in the Hagiwara synthesis of salvinorin A (**1**). After γ-hydroxylation and hydrogenation of the enone double bond, cyanohydrin formation opened the way to allyl alcohol **30**. In an Ireland-Claisen rearrangement, the quaternary stereocenter at C9 (salvinorin A numbering) was introduced. The desired isomer was obtained in 53% yield. This work might help to predict the stereochemical outcome of related rearrangements on decalin systems.

Experimental Section

General. All reactions were performed under nitrogen atmosphere. All solvents used in the reactions were purified before use. The progress of the reactions was followed by TLC (POLYGRAM SIL G/UV254). Flash chromatography was performed on silica gel Silica M, 0.04–0.63 mm, from Machery-Nagel GmbH & Co. KG, Germany. Distilled petroleum ether with a boiling range of 40–60 °C was used. Dry tetrahydrofuran and toluene were distilled from sodium and benzophenone, whereas CH_2Cl_2 was distilled from CaH_2. Methanol and Ethanol were used in HPLC grade quality. All commercially available compounds (abcr, Acros, Aldrich, Fluka, Merck and TCI) were used without purification. ^1H (400.160 MHz) and ^{13}C (100.620 MHz) spectra were recorded on a Bruker Avance 400 III HD spectrometer. $CDCl_3$ was used as solvent at room temperature. The ^1H NMR spectra were referenced to the residual signal of the non-deuterated solvent component ($CDCl_3$, 7.25 ppm) and the ^{13}C NMR spectra to the signal of the deuterated solvent ($CDCl_3$, 77.0 ppm). Peak assignments were made by NMR spectroscopy (^1H, ^{13}C, DEPT-135, H,H-COSY, HSQC, NOESY and HMBC). HRMS (ESI-TOF) analyses were performed on a Bruker maXis 4G system.

Deposition Numbers 2124065 (for **27**) and 2124065 (for **33 b**) contain the supplementary crystallographic data for this paper.

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These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

(3-Oxopentyl)-cyclohexane-1,3-dione (**22**). To a stirred solution of 2-methylcyclohexane-1,3-dione (1.89 g, 15.0 mmol, 1 equiv.) in ethyl acetate (100 mL) under N_2 were added ethyl vinyl ketone (1.63 mL, 16.5 mmol, 1.1 equiv.) and triethylamine (2.70 mL, 19.5 mmol, 1.3 equiv.) at room temperature. The resulting suspension was heated to 75 °C for 18 h. After cooling to room temperature, most of the solvent was evaporated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 3:2) to obtain triketone **22** as yellowish clear oil (2.64 g, 12.5 mmol, 84%). R_f = 0.24 (petroleum ether/ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.78–2.71 (m, 4H, 4-H, 6-H), 2.39 (q, J = 7.3 Hz, 2H, 4′-H), 2.33 (t, J = 7.5 Hz, 2H, 2′-H), 2.11–2.01 (m, 1H, 5-H), 2.07 (t, J = 7.5 Hz, 2H, 1′-H), 1.95–1.85 (m, 1H, 5-H), 1.24 (s, 3H, CH_3), 1.03 (t, J = 7.3 Hz, 3H, 11-H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 210.3 (C-3′), 210.1 (C-1, C-3), 64.4 (C-2), 37.7 (C-4, C-6), 37.0 (C-2′), 36.0 (C-4′), 29.8 (C-1′), 19.8 (C-5), 17.6 (CH_3), 7.7 (C-11).

(8a*R*)-5,8a-Dimethyl-1,2,3,4,6,7,8,8a-octahydronaphthalene-1,6-dione (**23**). To a stirred solution of (3-oxopentyl)-cyclohexane-1,3-dione **22** (1.50 g, 7.1 mmol, 1 equiv.) in dry DMF (105 mL) was added under N_2 D-phenylalanine (1.18 g, 7.1 mmol. 1 equiv.) and D-camphorsulfonic acid (0.83 g, 3.6 mmol, 0.5 equiv.). The resulting mixture was stirred for 24 h at room temperature. Thereafter, the mixture was heated to 40 °C for another 24 h. The temperature was raised 10 °C each day until 70 °C was reached. The mixture was allowed to reach room temperature and quenched with cold saturated aqueous $NaHCO_3$ (60 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×60 mL). The combined organic layers were washed with water (3×60 mL) and saturated NaCl solution (60 mL), then dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting orange oil was purified by flash chromatography (petroleum ether/ethyl acetate, 2:1) and subsequently by recrystallization (hexane/Et_2O, 5:1) at −20 °C to obtain diketone **23** (1.14 g, 6.0 mmol, 83%, 98% ee) as thin white needles. R_f = 0.33 (petroleum ether/ethyl acetate, 4:1); $[\alpha]_D^{25}$ = −137.3 (*c* 1.0, MeOH), lit.[17b] $[\alpha]_D^{25}$ = −139.0 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.92–2.85 (m, 1H, 4-H), 2.73–2.65 (m, 1H, 2-H), 2.55–2.41 (m, 4H, 7-H, 4-H, 2-H), 2.19–2.04 (m, 3H, 3-H, 8-H), 1.82 (d, J = 1.3 Hz, 3H, 5-CH_3), 1.80–1.72 (m, 1H, 3-H), 1.43 (s, 3H, 8a-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 212.2 (C-1), 197.7 (C-6), 158.1 (C-4a), 130.8 (C-5), 50.7 (C-8a), 37.4 (C-2), 33.3 (C-7), 29.6 (C-8), 27.3 (C-4), 23.4 (8a-CH_3), 21.5 (C-3), 11.3 (5-CH_3).

(8′a*R*)-5′,8′a-Dimethyl-3′,4′,6′,7′,8′,8′a-hexahydro-2′*H*-spiro[1,3-dioxolane-2,1′-naphthalen]-6′-one (**24**). In a flask equipped with a Dean-Stark trap, a stirred solution of ethlene glycol (6.33 mL, 11.3 mmol, 14.5 equiv.) in dry benzene (55 mL) was heated to reflux for 2 h under N_2 atmosphere. The trap was removed and the mixture allowed to reach room temperature. In a separate flask, diketone **23** (1.50 g, 7.8 mmol, 1 equiv.) was dissolved in benzene (15 mL) and added to the ethylene glycol solution over 10 min, followed by the addition of *p*TsOH (29.6 mg, 0.16 mmol, 0.02 equiv.). The resulting mixture was heated to reflux for an additional 2 h. After reaching room temperature, the reaction was quenched by addition of 1% aqueous $NaHCO_3$ (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×50 mL). The combined organic layers were washed with water and saturated NaCl solution (50 mL each), dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting yellow oil was purified by flash chromatography (petroleum ether/ethyl acetate, 2:1) to yield ketal **24** (1.73 g, 7.33 mmol, 94%) as colorless viscous oil. R_f = 0.31 (petroleum ether/ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.02–3.91 (m, 4H, OCH_2CH_2O), 2.77–2.72 (m, 1H, 8-H), 2.52–2.36 (m, 2H, 7-H), 2.29–2.07 (m, 2H, 4-H), 1.95–1.81 (m, 2H, 2-H, 3-H), 1.80 (dd, 3H, 5-CH_3), 1.73–1.61 (m, 3H, 2-H, 3-H, 8-H), 1.35 (s, 3H, 8a-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 198.7 (C-6), 160.1 (C-4a), 130.2 (C-5), 112.8 (C-1), 65.3 (OCH_2CH_2O), 65.1 (OCH_2CH_2O), 45.3 (C-8a), 33.7 (C-7), 29.7 (C-2), 26.5 (C-8), 26.4 (C-4). 21.4 (C-3), 20.9 (8a-CH_3), 11.5 (5-CH_3).

(4′*S*,8a′*R*)−4′-Hydroxy-5′,8a′-dimethyl-3′,4′,8′,8a′-tetrahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalen]-6′(7′*H*)-one (**6**). Catalyst preparation: To a stirred solution of $CuCl_2$ (10.0 g, 74.4 mmol) and $AlCl_3 \cdot 6H_2O$ (8.0 g, 60.0 mmol) in water (100 mL) was added a solution of Na_2CO_3 (2.54 g, 24.0 mmol) and NaOH (10.4 g, 260.0 mmol) in water (200 mL) over a period of 1.5 h. The resulting mixture was stirred at 77 °C for 22 h and subsequently filtered. The filter cake was washed with warm water. The black catalyst was dried at 95 °C overnight, finely crushed and left exposed to air for an additional 72 h.

The Cu–Al Ox catalyst (28.6 mg) was suspended in EtOH (1.7 mL) and the mixture stirred for 10 min open to air. Ketal **24** (100.0 mg, 0.42 mmol, 1 equiv.) in EtOH (0.3 mL) and *t*BuOK (59.4 mg, 0.53 mmol, 1.25 equiv.) were added followed by stirring of the mixture for 22 h at room temperature. Thereafter, the mixture was filtered through a pad of Celite, the filter cake was rinsed with MeOH and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 1:1) to give allylic alcohol **6** (62.8 mg, 0.25 mmol, 59%) as colorless oil. R_f = 0.17 (petroleum ether/ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.94 (t, J = 3.1 Hz, 1H, 4-H), 4.03–3.92 (m, 4H, OCH_2CH_2O), 2.59–2.46 (m, 2H, 7-H), 2.32–2.20 (m, 2H, 2-H, 8-H), 1.99–1.94 (m, 2H, 3-H), 1.88 (s, 3H, 5-CH_3), 1.72–1.66 (m, 1H, 8-H), 1.61–1.56 (dt, 1H, 2-H), 1.53 (s, 3H, 8a-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 199.7 (C-6), 158.1 (C-4a), 132.9 (C-5), 112.4 (C-1), 66.0 (C-4), 65.3 (OCH_2CH_2O), 65.0 (OCH_2CH_2O), 44.2 (C-8a), 33.6 (C-7), 28.9 (C-3), 27.3 (C-8), 24.6 (C-2), 22.5 (8a-CH_3), 11.0 (5-CH_3).

(4′*S*,8a′*R*)-5′,8a′-Dimethyl-4′-((triethylsilyl)oxy)-3′,4′,8′,8a′-tetrahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalen]-6′(7′*H*)-one (**25**). To a stirred solution of alcohol **6** (1.90 g, 7.5 mmol, 1 equiv.) in dry CH_2Cl_2 (20 mL) under N_2 were sequentially added imidazole (3.06 g, 45.0 mmol, 6 equiv.) and TESCl (3.78 mL, 22.5 mmol, 3 equiv.). The resulting mixture was stirred for 45 min at room temperature, then diluted with CH_2Cl_2 (20 mL) and finally treated with aqueous saturated $NaHCO_3$ (40 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to yield silyl ether **25** a colorless oil (3.18 g) which was used in the next step without any further purification. R_f = 0.73 (petroleum ether/ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.88 (t, J = 2.8 Hz, 1H, 4-H), 4.06–3.86 (m, 4H, OCH_2CH_2O), 2.60–2.41 (m, 2H, 7-H), 2.41–2.17 (m, 2H, 2-H, 8-H), 1.85 (s, 3H, 5-CH_3), 1.84–1.74 (m, 2H, 3-H), 1.73–1.55 (m, 1H, 2-H, 8-H), 1.53 (s, 3H, 8a-CH_3), 1.04–0.87 (m, 9H, $Si(CH_2CH_3)_3$), 0.70–0.50 (m, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 200.2 (C-6), 157.8 (C-4a), 131.4 (C-5), 112.8 (C-1), 66.5 (C-4), 65.3 (OCH_2CH_2O), 65.0 (OCH_2CH_2O), 45.0 (C-8a), 33.7 (C-7), 30.7 (C-3), 27.7 (C-8), 24.9 (C-2), 22.3 (8a-CH_3), 11.4 (5-CH_3), 6.8 ($Si(CH_2CH_3)_3$), 5.0 ($Si(CH_2CH_3)_3$); HRMS (ESI-TOF): calcd. for $C_{20}H_{34}O_4Si$ 389.21186 $[M+Na]^+$, found 389.21184.

(4′*S*,4a′*R*,5′*S*,8a′*R*)-5′,8a′-Dimethyl-4′-((triethylsilyl)oxy)hexahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalen]-6′(7′*H*)-one (**26**). Crude enone **25** (3.18 g) and 10% Pd/C (320 mg) in ethyl acetate (55 mL) were stirred under a H_2 atmosphere (1 atm) for 17 h. The resulting mixture was filtered through a pad of Celite, the filter cake was washed with ethyl acetate, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 12:1) to provide ketone **26** (2.41 g, 6.5 mmol, 87% over two steps) as a colorless oil. R_f = 0.59

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(petroleum ether/ethyl acetate, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.07–3.75 (m, 5H, OCH_2CH_2O, 4-H), 2.72 (td, J = 14.6 Hz, 6.1 Hz, 1H, 7-H_a), 2.56 (quint, J = 13.5, 7.0 Hz, 1H, 5-H), 2.28–2.08 (m, 2H, 2-H, 7-H), 2.00–1.85 (m, 2H, 4a-H, 8-H), 1.83–1.66 (m, 2H, 3-H), 1.64–1.60 (m, 1H, 8-H), 1.57 (s, 3H, 8a-CH_3), 1.48 (t, J = 3.0 Hz, 1H, 2-H), 1.43 (d, J = 7.7 Hz, 3H, 5-CH_3), 1.04–0.92 (m, 9H, $Si(CH_2CH_3)_3$), 0.63 (quart., J = 8.0 Hz, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 215.8 (C-6), 112.6 (C-1), 72.3 (C-4), 65.1 (OCH_2CH_2O), 64.9 (OCH_2CH_2O), 50.3 (C-5), 46.3 (C-4a), 42.6 (C-8a), 34.3 (C-7), 32.6 (C-3), 31.5 (C-8), 26.2 (C-2), 19.2 (8a-CH_3), 15.9 (5-CH_3), 7.0 ($Si(CH_2CH_3)_3$), 5.2 ($Si(CH_2CH_3)_3$); HRMS (ESI-TOF): calcd. for $C_{20}H_{36}O_4Si$ 391.22751 $[M+Na]^+$, found 391.22738.

(4′*S*,4a′*R*,5′*S*,6′*R*,8a′*R*)−6′-Hydroxy-5′,8a′-dimethyl-4′-((triethylsilyl)oxy)octahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalene]-6′-carbonitrile (**27**). To a stirred solution of ketone **26** (2.40 g, 6.5 mmol, 1 equiv.) in a mixture of DMSO/H_2O (5:1, 75 mL) was added TMSCN (2.46 mL, 19.5 mmol, 3 equiv.). The resulting mixture was stirred at room temperature for 19 h, after which time the solution was diluted with H_2O (150 mL). The aqueous layer was extracted with ethyl acetate (3×200 mL). The combined organic layers were washed with water and saturated NaCl solution (200 mL each), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1) to obtain cyanohydrin **27** (2.09 g, 5.3 mmol, 81%) as white solid. R_f = 0.50 (petroleum ether/ethyl acetate, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.15–3.76 (m, 5H, OCH_2CH_2O, 4-H), 2.37 (ddd, J = 7.3 Hz, 3.9, 1.5 Hz, 1H, 5-H), 2.14–2.04 (m, 1H, 2-H), 2.03–1.91 (m, 3H, 3-H, 4a-H), 1.91–1.79 (m, 2H, 7-H, 8-H), 1.66 (dq, J = 3.4 Hz, 13.8 Hz, 1 H, 7-H), 1.45 (td, J = 12.9, 3.3 Hz, 1H, 2-H), 1.36 (s, 3H, 8a-CH_3), 1.32 (d, J = 7.3 Hz, 3H, 5-CH_3), 1.29–1.23 (m, 1H, 8-H), 1.04–0.91 (m, 9H, $Si(CH_2CH_3)_3$), 0.69–0.54 (m, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 122.7 (CN), 112.1 (C-1), 74.0 (C-6), 72.8 (C-4), 65.2 (OCH_2CH_2O), 64.8 (OCH_2CH_2O), 44.1 (C-4a), 43.8 (C-5), 42.4 (C-8a), 32.5 (C-7), 28.8 (C-8), 28.7 (C-3), 26.1 (C-2), 19.4 (8a-CH_3), 10.6 (5-CH_3), 7.0 ($Si(CH_2CH_3)_3$), 5.1 ($Si(CH_2CH_3)_3$); HRMS (ESI-TOF): calcd. for $C_{21}H_{37}NO_4Si$ 418.23841 $[M+Na]^+$, found 418.23870.

(4′*S*,4a′*R*,8a′*R*)-5′,8a′-Dimethyl-4′-((triethylsilyl)oxy)-3′,4′,4a′,7′,8′,8a′-hexahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalene]-6′-carbonitrile (**28**). To a stirred solution of cyanohydrin **27** (1.00 g, 2.5 mmol, 1 equiv.) in dry toluene (60 mL) was added pyridine (0.82 mL, 10.1 mmol, 4 equiv.) under N_2 at room temperature. The solution was cooled to 0 °C and treated with $SOCl_2$ (0.37 mL, 5.1 mmol, 2 equiv.) over a period of 15 min. The resulting mixture was heated to reflux for 24 h and allowed to reach room temperature before being quenched by addition of water (60 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3× 60 mL). The combined organic layers were washed with saturated NaCl solution (60 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The orange residue was purified by flash chromatography (petroleum ether/ethyl acetate, 10:1) to yield unsaturated nitrile **28** (740.2 mg, 2.0 mmol, 78%) as yellow oil. R_f = 0.55 (petroleum ether/ethyl acetate, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.40–4.33 (m, 1H, 4-H), 4.02–3.80 (m, 4H, OCH_2CH_2O), 2.37–2.31 (m, 1H, 4a-H), 2.30–2.15 (m, 3H, 2-H, 7-H), 2.12 (s, 3H, 5-CH_3), 1.81–1.76 (m, 2H, 3-H), 1.58–1.44 (m, 3H, 2-H, 8-H), 1.14 (s, 3H, 8a-CH_3), 1.02–0.90 (m, 9H, $Si(CH_2CH_3)_3$), 0.68–0.55 (m, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 154.1 (C-5), 119.6 (CN), 112.2 (C-1), 106.7 (C-6), 67.0 (C-4), 65.3 (OCH_2CH_2O), 65.1 (OCH_2CH_2O), 49.2 (C-4a), 40.6 (C-8a), 31.5 (C-3), 27.3 (C-8), 25.9 (C-2), 24.7 (C-7), 20.0 (5-CH_3), 17.6 (8a-CH_3), 7.0 ($Si(CH_2CH_3)_3$), 5.3 ($Si(CH_2CH_3)_3$); HRMS (ESI-TOF): calcd. for $C_{21}H_{35}NO_3Si$ 400.22784 $[M+Na]^+$, found 400.22718.

(4′*S*,4a′*R*,8a′*R*)-5′,8a′-Dimethyl-4′-((triethylsilyl)oxy)-3′,4′,4a′,7′,8′,8a′-hexahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalene]-6′-carbaldehyde (**29**). A stirred solution of nitrile **28** (6.2 g, 16.3 mmol, 1 equiv.) in dry toluene (250 mL) was treated with DIBAL–H (1.0 M in hexane, 35 mL, 2.1 equiv.) under N_2 at −78 °C followed by stirring of the mixture for 4 h. Thereafter, the reaction was quenched at −78 °C by slow addition of 10% NaOH (150 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3×150 mL). The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 8:1) to yield aldehyde **29** (4.8 g, 12.6 mmol, 77%) as a colorless oil. R_f = 0.74 (petroleum ether/ethyl acetate, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 10.21 (s, 1H, CHO), 4.50 (q, J = 2.5 Hz, 1H, 4-H), 4.01–3.85 (m, 4H, OCH_2CH_2O), 2.44 (s, 1H, 4a-H), 2.40–2.34 (m, 1H, 7-H_a), 2.26 (s, 3H, 5-CH_3), 2.22–2.08 (m, 2H, 2-H, 7-H), 1.86–1.76 (m, 2H, 3-H), 1.55–1.47 (m, 3H, 2-H, 8-H), 1.11 (s, 3H, 8a-CH_3), 1.01–0.92 (m, 9H, $Si(CH_2CH_3)_3$), 0.69–0.53 (m, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 191.6 (CO), 156.6 (C-5), 133.9 (C-6), 112.5 (C-1), 66.8 (C-4), 65.3 (OCH_2CH_2O), 65.1 (OCH_2CH_2O), 50.8 (C-4a), 40.7 (C-8a), 31.7 (C-3), 27.1 (C-8), 26.1 (C-2), 19.9 (C-7), 17.8 (8a-CH_3), 14.2 (5-CH_3), 7.0 ($Si(CH_2CH_3)_3$), 5.4 ($Si(CH_2CH_3)_3$); HRMS (ESI-TOF): calcd. for $C_{21}H_{36}NO_4Si$ 403.22751 $[M+Na]^+$, found 403.22744.

((4′*S*,4a′*R*,8a′*R*)-5′,8a′-Dimethyl-4′-((triethylsilyl)oxy)-3′,4′,4a′,7′,8′,8a′-hexahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalen]-6′-yl)methanol (**30**). To a stirred solution of aldehyde **29** (108 mg, 0.28 mmol, 1 equiv.) in a mixture of THF/H_2O (10:1, 3 mL) was added $NaBH_4$ (32 mg, 0.9 mmol, 3 equiv.) portion-wise at 0 °C over a period of 15 min. The reaction mixture was stirred for 2 h at 0 °C and subsequently quenched by addition of aqueous NH_4Cl (5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 3:1) to yield alcohol **30** (74 mg, 0.2 mmol, 68%) as white solid. R_f = 0.38 (petroleum ether/ethyl acetate, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.37 (d, J = 2.6 Hz, 1H, 4-H), 4.26–4.09 (m, 1H, CH_2OH), 4.04–3.85 (m, 5H, CH_2OH, OCH_2CH_2O), 2.26 (br s, 1H, 4a-H), 2.21–2.12 (m, 3H, 2-H, 7-H), 1.89–1.69 (m, 5H, 3-H, 5-CH_3), 1.60–1.41 (m, 3H, 2-H, 8-H), 1.15 (s, 3H, 8a-CH_3), 1.02–0.89 (m, 9H, $Si(CH_2CH_3)_3$), 0.70–0.52 (m, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 131.4 (C-6), 130.0 (C-5), 113.0 (C-1), 67.4 (C-4), 65.2 (OCH_2CH_2O), 65.0 (OCH_2CH_2O), 63.6 (CH_2OH), 48.6 (C-4a), 40.7 (C-8a), 31.9 (C-3), 28.2 (C-8), 26.2 (C-2), 25.4 (C-7), 17.6 (8a-CH_3), 14.9 (5-CH_3), 7.0 ($Si(CH_2CH_3)_3$), 5.4 ($Si(CH_2CH_3)_3$); HRMS (ESI-TOF): calcd. for $C_{21}H_{38}O_4Si$ 405.24316 $[M+Na]^+$, found 405.24363.

((4′*S*,4a′*R*,8a′*R*)-5′,8a′-Dimethyl-4′-((triethylsilyl)oxy)-3′,4′,4a′,7′,8′,8a′-hexahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalen]-6′-yl)methyl acetate (**31**). A solution of alcohol **30** (30 mg, 78.4 μmol) in a mixture of pyridine/Ac_2O (1:2, 0.45 mL) was stirred under N_2 for 2 h. After this time, the reaction was quenched by addition of water (1 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 10:1) to yield acetate **31** (23 mg, 54.2 μmol, 69%) as a colorless oil. R_f = 0.51 (petroleum ether/ethyl acetate, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.64 (d, J = 11.8 Hz, 1H, CH_2OAc), 4.50 (d, J = 12.0 Hz, 1H, CH_2OAc), 4.43–4.34 (m, 1H, 4-H), 4.02–3.92 (m, 4H, OCH_2CH_2O), 2.29 (br s, 1H, 4a-H), 2.21–2.09 (m, 3H, 2-H, 7-H), 2.05 (s, 3H, O_2CCH_3), 1.81–1.75 (m, 5H, 3-H, 5-CH_3), 1.57 (td, J = 12.3, 6.5 Hz, 1H, 8-H), 1.51–1.45 (m, 1H, 2-H), 1.44–1.39 (m, 1H, 8-H) 1.14 (s, 3H, 8a-CH_3), 0.94 (t, J = 8.0 Hz, 9H, $Si(CH_2CH_3)_3$), 0.62–0.54 (qd, J = 8.2, 3.2 Hz, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 171.4 (O_2CCH_3), 133.9 (C-6), 125.4 (C-5), 113.0 (C-1), 67.4 (C-4), 65.2 (OCH_2CH_2O), 65.0 (CH_2OAc), 48.7 (C-4a), 40.7 (C-8a), 31.9 (C-3), 28.1 (C-8), 26.2 (C-2), 25.7 (C-7), 21.0 (O_2CCH_3), 17.6 (8a-CH_3), 15.3 (5-CH_3),

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7.0 ($Si(CH_2CH_3)_3$), 5.4 ($Si(CH_2CH_3)_3$); HRMS (ESI-TOF): calcd. for $C_{23}H_{40}O_5Si$ 447.25372 $[M+Na]^+$, found 447.25366.

Ethyl 2-((4′*S*,4a′*R*,5′*R*,8a′*R*)-5′,8a′-dimethyl-6′-methylene-4′-((triethylsilyl)oxy)octahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalen]-5′-yl)acetate (**33 a**) and its epimer (**33 b**). To a stirred solution of alcohol **30** (500 mg, 1.31 mmol, 1 equiv.) in dry *o*-DCB (4.8 mL) were sequentially added hydroquinone (72 mg, 0.65 mmol, 0.5 equiv.) and triethyl orthoacetate (4.8 mL, 26.1 mmol, 20 equiv.). The resulting mixture was heated to 180 °C for 17 h. Thereafter, the reaction mixture was allowed to reach room temperature and quenched by addition of water (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with aqueous $NaHCO_3$ solution, saturated NaCl solution (15 mL each), dried over Na_2SO_4, filtered and concentrated in vacuo. The brown residue was purified by flash chromatography (petroleum ether/ethyl acetate, 30:1) to yield ester **33 a** (312 mg, 0.69 mmol, 52%) as a viscous oil and its C5 epimer **33 b** (119 mg, 0.26 mmol, 20%) as colorless needles.

33 a: R_f = 0.51 (petroleum ether/ethyl acetate, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.79–4.58 (m, 2H, 6-CH_2), 4.39 (d, *J* = 2.1 Hz, 1H, 4-H), 4.10 (dq, *J* = 7.1, 2.9 Hz, 2H, O*C*$H_2$$CH_3$), 3.98–3.80 (m, 4H, OCH_2CH_2O), 2.66, 2.59 (2d, *J* = 16.0 Hz, 2H, CH_2CO_2Et), 2.48 (td, *J* = 13.9, 4.3 Hz, 1H, 7-H), 2.32 (d, *J* = 1.8 Hz, 1H, 4a-H), 2.19–2.03 (m, 2H, 2-H, 7-H), 1.83–1.59 (m, 3H, 3-H, 8-H_a), 1.50 (s, 3H, 8a-CH_3), 1.46–1.32 (m, 2H, 2-H_b, 8-H_b) 1.36 (s, 3H, 5-CH_3), 1.24 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.03–0.91 (m, 9H, $Si(CH_2CH_3)_3$), 0.70–0.57 (m, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 171.6 (CO_2Et), 155.4 (C-6), 113.2 (C-1), 105.0 (6-CH_2), 68.6 (C-4), 65.2 (OCH_2CH_2O), 64.9 (OCH_2CH_2O), 59.8 (OCH_2CH_3), 46.5 (C-4a), 44.0 (C-8a), 43.8 (C-5), 43.1 (CH_2CO_2Et), 32.7 (C-8), 32.4 (C-3), 29.6 (C-7), 26.6 (5-CH_3), 26.0 (C-2), 19.7 (8a-CH_3), 14.2 (OCH_2CH_3), 7.1 ($Si(CH_2CH_3)_3$), 5.4 ($Si(CH_2CH_3)_3$); HRMS (ESI-TOF): calcd. for $C_{25}H_{44}O_5Si$ 475.28502 $[M+Na]^+$, found 475.28491.

33 b: R_f = 0.45 (petroleum ether/ethyl acetate, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.79–4.59 (m, 2H, 6-CH_2), 4.47 (d, *J* = 2.3 Hz, 1H, 4-H), 4.02 (dq, *J* = 7.2, 3.9 Hz, 2H, O*C*$H_2$$CH_3$), 3.96–3.80 (m, 4H, OCH_2CH_2O), 3.02, 2.87 (2d, *J* = 13.1 Hz, 2H, CH_2CO_2Et), 2.59 (td, *J* = 13.3, 3.9 Hz, 1H, 7-H), 2.20–2.02 (m, 2H, 2-H, 7-H), 1.76–1.64 (m, 2H, 3-H), 1.61–1.51 (m, 1H, 8-H), 1.55 (s, 3H, 8a-CH_3), 1.47 (t, *J* = 3.7 Hz, 1H, 8-H), 1.43 (t, *J* = 3.5 Hz, 1H, 2-H), 1.39 (d, *J* = 1.8 Hz, 1H, 4a-H), 1.31 (s, 3H, 5-CH_3), 1.20 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.03–0.95 (m, 9H, $Si(CH_2CH_3)_3$), 0.71–0.63 (m, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 172.6 (CO_2Et), 154.4 (C-6), 113.2 (C-1), 106.9 (6-CH_2), 68.1 (C-4), 65.2 (OCH_2CH_2O), 64.8 (OCH_2CH_2O), 59.6 (OCH_2CH_3), 54.2 (C-4a), 44.1 (C-8a), 42.8 (C-5), 41.2 (CH_2CO_2Et), 34.0 (C-8), 32.5 (C-3), 29.6 (C-7), 26.0 (C-2), 24.7 (5-CH_3), 19.4 (8a-CH_3), 14.2 (OCH_2CH_3), 7.0 ($Si(CH_2CH_3)_3$), 5.4 ($Si(CH_2CH_3)_3$); HRMS (ESI-TOF): calcd. for $C_{25}H_{44}O_5Si$ 475.28502 $[M+Na]^+$, found 475.28479.

Ethyl 2-((4′*S*,4a′*R*,5′*R*,8a′*R*)-5′,8a′-dimethyl-6′-oxo-4′-((triethylsilyl)oxy)octahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalen]-5′-yl)acetate (**36**). Through a stirred solution of acetate **33 a** (27.0 mg, 59.5 μmol, 1 equiv.) in a mixture of MeOH/CH_2Cl_2 (3:1) was bubbled ozone at −78 °C. After 1 h, the reaction mixture was purged with argon, quenched by addition of Me_2S (0.2 mL) and subsequently concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1) to yield keto ester **36** (18.4 mg, 40.5 μmol, 68%) as colorless oil. R_f = 0.30 (petroleum ether/ethyl acetate, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.21 (d, *J* = 1.8 Hz, 1H, 4-H), 4.10 (dddd, *J* = 25.5, 18.5, 7.2, 3.7 Hz, 2H, O*C*$H_2$$CH_3$), 4.01–3.84 (m, 4H, OCH_2CH_2O), 2.99 (d, *J* = 16.8 Hz, 1H, CH_2CO_2Et), 2.67–2.53 (m, 1H, 7-H), 2.50–2.36 (m, 2H, CH_2CO_2Et, 7-H), 2.33 (d, *J* = 1.5 Hz, 1H, 4a-H), 2.10 (m, 2H, 2-H, 8-H), 1.76–1.44 (m, 4H, 2-H, 3-H, 8-H), 1.54 (s, 3H, 8a-CH_3), 1.34 (s, 3H, 5-CH_3), 1.24 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 0.98 (t, *J* = 8.3 Hz, 9H, $Si(CH_2CH_3)_3$), 0.65 (q, *J* = 7.9 Hz, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 214.9 (C-6), 171.7 (CO_2Et), 112.8 (C-1), 68.5 (C-4), 65.2 (OCH_2CH_2O), 65.1 (OCH_2CH_2O), 60.4 (OCH_2CH_3), 50.4 (C-5), 47.0 (C-4a), 43.0 (C-8a), 42.7 (5-CH_2), 34.9 (C-7), 32.7 (C-3), 29.2 (C-8), 26.0 (C-2), 24.6 (5-CH_3), 19.4 (8a-CH_3), 14.2 (OCH_2CH_3), 7.1 ($Si(CH_2CH_3)_3$), 5.4 ($Si(CH_2CH_3)_3$); HRMS (ESI-TOF): calcd. for $C_{24}H_{42}O_6Si$ 477.26429 $[M+Na]^+$, found 477.26425.

Ethyl 2-((1*R*,4a*R*,8*S*,8a*S*)−1,4a–dimethyl-2,5-dioxo-8-((triethylsilyl)oxy)decahydronaphthalen-1-yl)acetate (**37**). To a stirred solution of ester **36** (10.00 mg, 22.0 μmol, 1 equiv.) in EtOH (0.5 mL) was added 3 M HCl (0.17 mL). The resulting mixture was stirred at room temperature for 3 h and subsequently quenched by addition of saturated aqueous $NaHCO_3$ solution (2 mL). The aqueous layer was extracted with Et_2O (3 mL). The combined organic layers were washed with water and saturated NaCl solution (5 mL each), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The yellow residue was purified by flash chromatography (petroleum ether/ethyl acetate, 6:1) to yield ester **37** (7.4 mg, 18.0 μmol, 82%) as a colorless oil. R_f = 0.71 (petroleum ether/ethyl acetate, 6:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.36 (br s, 1H, 4-H), 4.06 (dddd, *J* = 17.5, 10.4, 7.2, 3.7 Hz, 2H, O*C*$H_2$$CH_3$), 3.06 (dt, *J* = 6.1, 14.3 Hz, 1H, 6-H), 3.03 (d, *J* = 17.2 Hz, 1H, CH_2CO_2Et), 2.67–2.54 (m, 1H, 3-H), 2.51–2.45 (m, 2H, 3-H), 2.46 (d, *J* = 17.2 Hz, 1H, CH_2CO_2Et), 2.27 (d, *J* = 1.1 Hz 1H, 8a-H), 2.23 (ddd, *J* = 14.2, 2.5, 1.7 Hz, 1H, 6-H), 2.10 (ddd, *J* = 14.1, 3.2, 2.6 Hz, 1H, 7-H), 1.97 (dd, *J* = 9.9, 3.8 Hz, 2H, 4-H), 1.78 (ddt, *J* = 4.3, 2.5, 1.8 Hz, 1H, 7-H), 1.63 (s, 3H, 4a-CH_3), 1.41 (s, 3H, 1-CH_3), 1.22 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.02 (t, *J* = 8.3 Hz, 9H, $Si(CH_2CH_3)_3$), 0.70 (q, *J* = 7.9 Hz, 6H, $Si(CH_2CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) = 213.7 (C-2), 213.3 (C-5), 171.4 (CO_2Et), 67.8 (C-8), 60.5 (OCH_2CH_3), 50.6 (C-1), 49.5 (C-8a), 48.3 (C-4a), 42.3 (CH_2CO_2Et), 35.2 (C-7), 34.5 (C-3), 32.9 (C-6), 31.9 (C-4), 24.3 (1-CH_3), 20.9 (4a-CH_3), 14.1 (OCH_2CH_3), 7.1 ($Si(CH_2CH_3)_3$), 5.3 ($Si(CH_2CH_3)_3$); HRMS (ESI-TOF): calcd. for $C_{22}H_{38}O_5Si$ 433.23807 $[M+Na]^+$, found 433.23783.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: cyanohydrin · decalins · Johnson-Claisen rearrangement · salvinorin A · Wieland-Miescher ketone

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