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Standard Protecting Groups Create Potent and Selective κ Opioids: Salvinorin B Alkoxymethyl Ethers

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Abstract

Protection of salvinorin B as standard alkoxyalkyl ethers yielded highly potent κ opioid receptor agonists. Ethoxymethyl ether **6** is among the most potent and selective κ agonists reported to date. Fluoroethoxymethyl ether **11** is the first potent, selective fluorinated κ ligand, with potential use in MRI and PET studies. Further enlargement of the alkoxy group, alkylation of the acetal carbon, or heteroatom substitution all reduced activity. These protecting groups may prove useful in related work not only by enabling the use of harsher synthetic conditions, but potentially by optimizing the potency of the products.

Keywords

Salvinorin A; Kappa opioid receptor; Methoxymethyl ether; Protecting groups

1. Introduction

Salvinorin A (**1**) is a potent and selective naturally-occurring κ (kappa) opioid.[1] As one of very few reported non-nitrogenous opioids,[2] salvinorin A has created new opportunities for understanding the mechanisms of ligand binding at opioid receptors, which might facilitate drug discovery. One objective has been the development of selective antagonists or partial agonists at κ opioid receptors; such agents have potential utility in the treatment of depression or mania,[3] debilitating conditions for which all current treatments have significant limitations (e.g., poor efficacy, delayed onset, marked side effects). Many derivatives of **1** have now been tested at opioid receptors.[4] Binding affinity and potency are almost invariably reduced; very few derivatives exhibit potency comparable to **1**. Most active derivatives, like the parent compound, are full agonists, but recently partial agonists and antagonists have been reported.[4,5] This is potentially significant, since the few available selective κ antagonists exhibit extremely slow onset (~24 hr) and long duration of action (>3 weeks),[6] which complicates their use in the study or treatment of psychiatric conditions such as depression.[7] However, the modifications which appear to confer partial agonist and antagonist activities on salvinorin

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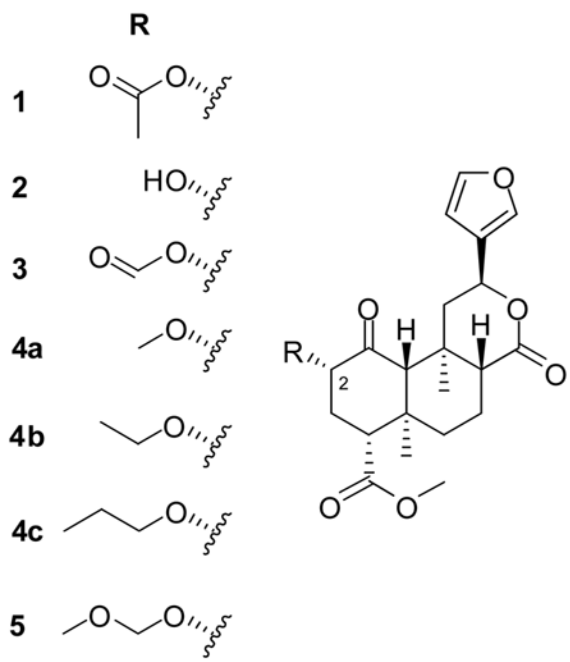
derivatives also dramatically reduce binding affinity and selectivity;[4,5] methods to optimize these parameters would therefore be useful.



To date the most thoroughly studied functional group of **1** is the C-2 acetate. Interestingly, while deacetylation (giving **2**) dramatically lowers affinity and potency,[8] demethyl and deoxy analogues **3**[9] and **4b**[8] each show only modestly reduced affinity. This suggests that these two portions of the acetate may be involved in separate, synergistic interactions with the receptor. Only one derivative with greater potency than **1** has been reported to date: methoxymethyl (MOM) ether **5**.[10] The increased affinity of **5** may be due to the additional sp^3-hybridized oxygen, especially considering the lower affinity of its closest sp^2-hybridized analogue, **3**. Alternatively, the terminal methyl group of **5** might create an additional interaction, which could be explored by the substitution of other alkoxy groups. A related question is whether methylation of the acetal carbon would further increase potency, as with formate **3**. In hopes of optimizing the C-2 substituent, we explored these questions using related protecting groups.

2. Chemistry

Deacetylation[11] of **1**, isolated from dried *Salvia divinorum* leaves as previously described,[12] gave **2**. MOM ether **5** was prepared from **2** and CH_3OCH_2Cl as previously described.[13] The published ^{1}H NMR data[13] required amendment. The molecular formula, not previously established, was confirmed by HRMS. The ethoxymethyl (EOM) ether **6** and several other standard alkoxymethyl ethers were prepared similarly (Scheme 1; see Table 1 for individual structures).[14]

For the more unusual alkoxymethyl ethers **7–12**, the corresponding chloromethyl ethers were expensive or hard to obtain. Rather than prepare and purify these volatile carcinogens, an alternative route was used. Methylthiomethyl ether **16** was prepared from **2** using Ac_2O and AcOH in Me_2SO (Scheme 1).[15] When following the published procedure, side reactions resulted in poor yields, but we found that these were suppressed by a large excess of AcOH. The alkoxymethyl compounds **7–12** were then produced by alcoholysis of **16**, using *N*-iodosuccinimide (NIS) and catalytic TfOH with the appropriate alcohol.[16] Although lowyielding (< 40%), this route offers access to a wide range of products from a common intermediate and readily available alcohols. The NIS route was also employed for the 2-methoxyethoxymethyl (MEM) ether **13**. Although the corresponding chloromethyl ether is readily available, **13** is difficult to separate from residual starting material **2**, making purification difficult; the NIS route from **16** circumvented this difficulty, since **13** and **16** are easily separated. Due to the low yields of the NIS/TfOH route, other conditions were tested ($AgNO_3$/2,6-lutidine17 and $HgCl_2$);18 unfortunately, neither proved effective. Fluoromethyl ether **17** was prepared using a closely related method: NIS and Et_2NSF_3.19 Typical $^1J_{CF}$ and $^2J_{HF}$ couplings were observed in the ^{1}H, ^{13}C and ^{19}F NMR spectra of all fluorinated compounds (**11**, **12** and **17**).

Compounds **18**, **19**, and **20** were prepared using ethoxyethene, 2-methoxypropene, and 3,4-dihydro-2*H*-pyran, respectively, with catalytic *p*-TsOH or PPTS (Scheme 2).[14] The two epimers of **18** were separated with difficulty by repeated flash chromatography; complete separation was not achieved. Epimerization also occurred in $CDCl_3$, so NMR data were collected in C_6D_6. The relative configurations of **18a** and **b** were not determined. Tetrahydropyranyl ether **20** was also formed as an epimeric mixture, but only one epimer could be isolated after chromatography on silica gel, contaminated with a small amount of the other. Again, the configuration at the acetal carbon is unknown. For NMR, $CDCl_3$ filtered through basic Al_2O_3 was satisfactory for brief exposures, but for longer experiments C_6D_6 was required.

3. Results and Discussion

Binding affinities and potencies at the κ receptor are shown in Table 1. All compounds were full agonists, with efficacy approximately equal to that of U50,488H. All compounds except **14** showed submicromolar affinity and potency, generally in the low nanomolar range. None of the compounds bound to μ or δ receptors (K_i > 1 μM). This series as a whole shows markedly higher affinity and selectivity than previously reported series of derivatives of **1**.

Among the *n*-alkoxymethyl ethers **5–8**, the ethyl substituent was optimal (**6**), conferring extreme (subnanomolar) affinity and potency. Given the lack of μ and δ affinity, this compound is therefore also extremely selective (μ/κ and δ/κ > 3,000). There have been very few reports of compounds with μ/κ selectivity over 1,000.[20] Ethoxymethyl ether **6** is thus among the most potent and selective κ opioids reported to date. While the naltrexone derivative nalfurafine (TRK-820) is more potent still (EC_{50} = 0.025 nM under the same conditions), this compound shows much lower selectivity (μ/κ < 100).[21]

The potency of the MOM ether **5**, while lower than **6**, was nonetheless higher than **1** or U50,488H, as previously reported.[10] The selectivity of this compound, which has not previously been quantified, is thus also extremely high (μ/κ and δ/κ > 1,600). Further extension of the alkyl chain reduced activity, but the propoxymethyl and butoxymethyl ethers **7** and **8** retained activity comparable to **1**. The same trend was previously reported in the alkyl ether[8] and ester[22] series, but with strikingly inferior absolute values. This provides further confirmation that substitution of oxygen in this position dramatically increases binding affinity. However, the increase in binding affinity from **5** to **6** suggests that an additional interaction involving the terminal alkyl group also contributes to the extremely high affinities of these compounds. For instance, the receptor may possess a hydrophobic pocket just deep enough to accommodate an ethyl group.

Branching of the alkyl chain was not as well tolerated as elongation; the isopropoxy and *tert*-butoxy compounds **9** and **10** showed a steep, progressive loss of activity relative to **6**. MEM ether **13**, with the same chain length as butoxymethyl ether **8**, showed lower affinity than that compound. Larger protecting groups were also poorly tolerated: the 2-(trimethylsilyl) ethoxymethyl (SEM, **14**) and benzyloxymethyl (BOM, **15**) ethers were the least active compounds in the series.

2-Fluoroethoxymethyl ether **11** showed potency and affinity approximately equal to salvinorin A (**1**) itself. To our knowledge, **11** is the first potent, selective fluorinated ligand at the κ opioid receptor to be reported in the peer-reviewed literature. This is potentially significant, since the presence of fluorine permits *in vivo* imaging through ^{19}F magnetic resonance imaging (MRI), or (with ^{18}F labeling) positron emission tomography (PET).[23] Should labeling prove feasible, compound **11** has important potential advantages over the existing [^{11}C]-labelled PET ligand, GR103545.[24] Although often described as κ-selective, that compound and its racemate in fact display higher affinity for μ than κ receptors (μ/κ = 0.5).[25] By contrast, compound **11** is highly selective (μ/κ > 500). Another potential advantage of **11** is that the half-life of ^{18}F is five times longer than that of ^{11}C, which increases sensitivity and allows a wider range of experiments.

Heteroatom substitution at the alkoxy group reduced activity. Methylthiomethyl ether **16** showed much lower potency than **5**, comparable to the previously-reported propyl ether **4c** of equal chain length (EC_{50} = 67 nM under the same conditions).[8] The potency of fluoromethyl ether **17** was also greatly reduced relative to **5**. Although fluorine is widely regarded as isosteric with hydrogen, it is in fact much closer in size to oxygen, and can serve as an effective bioisostere for hydroxy and methoxy groups.[26] Thus, while many would regard **17** as a bioisostere for the methyl ether **4a**, it is in fact closer to **5**. Direct comparison of fluorine and oxygen is confounded, however, by the terminal methyl substituent in **5**, which as discussed above appears to contribute to that compound's potency. An indirect comparison is nonetheless possible. The potency of **17** was similar to that of ethyl ether **4b** (EC_{50} = 18 nM).[8] Thus, whereas substitution of oxygen for C-2 of the propyl and butyl ethers (giving **5** and **6**) dramatically increases activity, substitution of fluorine for C-2 of the ethyl ether (giving **17**) has little effect. These results for **16** and **17** suggest that the alkoxymethyl group may act as an H-bond acceptor, since organic fluorine is a very poor H-bond acceptor,[27] and sulfur is not an acceptor.

Contrary to the trend observed with the formate **3**, methyl substitution of the acetal carbon dramatically lowered affinity. Compound **18** (the methyl analogue of **6)**, had at least 20-fold lower affinity, while **19** (the dimethyl analogue of **5**) exhibited a greater than 100-fold reduction. This implies that this series of compounds may bind in a different manner than the ester series. The tetrahydropyranyl ether **20** showed comparable affinity to **1**; thus, monosubstitution of the acetal carbon is better tolerated than disubstitution. There was not a dramatic difference in potency between the epimers of **18**; unfortunately, only one epimer of **20** could be isolated, preventing any additional investigation of this question.

The high affinities of the alkoxymethyl ethers are of particular interest because these protecting groups are more stable than acetates under many synthetic conditions. For instance, **1** is readily deacetylated by weak bases, and the α-hydroxy ketone function thus exposed is highly sensitive to strong bases,[12] while MOM ethers are virtually inert under strongly basic conditions.[14] Similarly, MOM ethers are generally more stable to nucleophiles, organometallic and hydride reagents than acetates.[14] A very pertinent illustration of these advantages is the first total synthesis of **1**, which employs a BOM protecting group at C-2 in place of the acetate.[28]

4. Conclusions

It is fortuitous that standard protecting groups, stable and unreactive under a wide range of harsh conditions, should also confer high potency. For synthetic transformations elsewhere in the salvinorin scaffold, this permits the use of conditions incompatible with an acetate or hydroxyl. The resulting derivatives may also possess higher affinity and selectivity than the corresponding acetate, which would be valuable in ameliorating the effects of transformations elsewhere in the parent compound. For instance, some salvinorin derivatives appear to exhibit antagonism or partial agonism,[4,5] but this is accompanied by severe reductions in affinity and selectivity. In such cases, it would be interesting to explore whether a C-2 alkoxymethyl ether substituent attenuated these reductions in affinity and selectivity. Alkoxymethyl ethers are also likely to be more stable *in vivo*, which would be desirable given salvinorin A's brief duration of action. In a recent report, a MOM ether showed equal *in vitro* activity against HIV to the corresponding acetate, and greater stability in plasma.[29]

5. Experimental

5.1. General Experimental Conditions

^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) chemical shifts are referenced to residual solvent peaks as internal standards: $CDCl_3$ (7.26 and 77 ppm), C_6D_6 (7.16 and 128 ppm), and C_6D_5N (135.5 ppm). 19F NMR chemical shifts are referenced to CCl_3F (0 ppm). Where the coupling constants of a discrete multiplet could not be determined, the separation of the outermost peaks (Δν) is given in Hz. Flash column chromatography (FCC) was performed on silica gel (230–400 mesh, 60 Å), eluting with a stepped gradient over the specified range. Where compound **2** was present due to incomplete reaction or hydrolysis of products, the column was stripped with 20% $MeOH/CH_2Cl_2$ to maximize recovery.

5.2. Binding Assays

Binding affinities at μ, δ, and κ opioid receptors were determined, as previously described,[21] by competitive inhibition of [^{3}H]diprenorphine binding to membranes prepared from Chinese hamster ovary (CHO) cells stably transfected with the human κ (hKOR), rat μ, or mouse δ receptors. Compounds were initially screened at 3 μM; those compounds causing > 50% displacement of [^{3}H]diprenorphine (equivalent under the assay conditions to K_i < 1 μM) were tested further for determination of binding affinity (K_i), potency (EC_{50}) and efficacy (E_{max}). Positive controls were U50,488H (κ), DAMGO (μ), SNC80 (δ), and etorphine (μ/δ), which all caused > 90% displacement of [^{3}H]diprenorphine at 3 μM. Potencies and efficacies were determined by [^{35}S]GTPγS binding to membranes of CHO-hKOR cells, as previously described.[21] Testing was blinded: neither identity nor molecular mass were known to the testers.

5.3. Salvinorin B methoxymethyl ether (5)

Prepared as previously described.[13] **TLC (50% EtOAc/hexanes):** hR_f = 40 (**5**), 30 (**2**); **1H NMR ($CDCl_3$):** δ 7.41 (1H, dt, *J* = 1.8, 0.9 Hz), 7.40 (1H, t, *J* = 1.8 Hz), 6.38 (1H, dd, *J* = 1.8, 0.9 Hz), 5.54 (1H, dd, *J* = 11.8, 5.2 Hz), 4.72 (1H, d, *J* = 7.0 Hz), 4.70 (1H, d, *J* = 7.0 Hz), 4.14 (1H, dd, *J* = 12.2, 7.4 Hz), 3.71 (3H, s), 3.38 (3H, s), 2.68 (1H, dd, *J* = 13.5, 3.5 Hz), 2.53 (1H, dd, *J* = 13.5, 5.3 Hz), 2.36 (1H, ddd, *J* = 13.5, 7.6, 3.6 Hz), 2.19 (1H, td, *J* = 13.4, 12.2 Hz), 2.15 (1H, dq, *J* = 13.5, 3.4 Hz), 2.06 (1H, br s), 2.05 (1H, dd, *J* = 11.3, 3.2 Hz), 1.78 (1H, m, Δν = 18.6 Hz), 1.71–1.45 (3H, m), 1.46 (3H, s), 1.11 (3H, s); **^{13}C NMR ($CDCl_3$):** δ 205.8, 171.8, 171.2, 143.7, 139.4, 125.3, 108.3, 95.7, 77.8, 71.9, 64.3, 55.8, 53.8, 51.9, 51.5, 43.5, 41.9, 38.1, 35.5, 32.6, 18.1, 16.4, 15.2; **HRMS(ESI):** $[M+NH_4]^+$ *m/z* 452.2295 (calcd for $C_{23}H_{30}O_8$, 452.2284).

5.4. Salvinorin B ethoxymethyl ether (6)

Salvinorin B (**2**) (49.7 mg, 127 μmol) was added to dry DMF (1 mL) under Ar with warming. *i*-Pr_2NEt (110 μL, 631 μmol) and $EtOCH_2Cl$ (60 μL, 646 μmol) were added. The white slurry was stirred at r.t. for 24 h. The solution was diluted in EtOAc and washed with 0.1 M aq. HCl

(× 3), H_2O, sat. aq. $NaHCO_3$, and brine and dried ($MgSO_4$). FCC (25–50% EtOAc/hexanes, then 20% MeOH/CH_2Cl_2) gave **6** as an amorphous white solid (45.6 mg, 80%). **TLC (50% EtOAc/hexanes):** hR_f = 47 (**6**), 30 (**2**); **1H NMR ($CDCl_3$):** δ 7.41 (1H, dt, J = 1.6, 0.9 Hz), 7.40 (1H, t, *J* = 1.8 Hz), 6.37 (1H, dd, *J* = 1.8, 0.9 Hz), 5.54 (1H, dd, *J* = 11.6, 5.1 Hz), 4.77 (1H, d, *J* = 7.0 Hz), 4.74 (1H, d, *J* = 7.0 Hz), 4.16 (1H, dd, *J* = 12.1, 7.4 Hz), 3.71 (3H, s), 3.69 (1H, dq, J = 9.7, 7.0 Hz), 3.58 (1H, dq, J = 9.7, 7.0 Hz), 2.69 (1H, dd, *J* = 13.3, 3.4 Hz), 2.53 (1H, dd, *J* = 13.3, 5.1 Hz), 2.34 (1H, ddd, *J* = 13.5, 7.4, 3.5 Hz), 2.18 (1H, td, *J* = 13.4, 12.1 Hz), 2.15 (1H, dq, *J* = 13.7, 3.5 Hz), 2.06 (1H, br s), 2.05 (1H, m, Δν = 15 Hz), 1.77 (1H, m, Δν = 18.3 Hz), 1.71–1.44 (3H, m), 1.46 (3H, s), 1.18 (3H, t, *J* = 6.9 Hz), 1.11 (3H, s); **^{13}C NMR ($CDCl_3$):** δ 206.0, 171.8, 171.2, 143.7, 139.3, 125.3, 108.3, 94.3, 77.7, 71.9, 64.2, 63.8, 53.8, 51.8, 51.4, 43.4, 41.9, 38.1, 35.4, 32.6, 18.1, 16.4, 15.2, 15.1; **HRMS(ESI):** $[M+H]^+$ *m/z* 449.2193 (calcd for $C_{24}H_{32}O_8$, 449.2175).

5.5. Salvinorin B propoxymethyl ether (7)

Propanol was stored over freshly activated 4 Å sieves for 1 h. To a mixture of methylthiomethyl ether **16** (37.6 mg, 83.5 μmol), *N*-iodosuccinimide (28.6 mg, 127 μmol, 1.5 eq), and 4 Å molecular sieves (beads) under Ar was added CH_2Cl_2 (0.5 mL). The flask was cooled to 0 ° C, and dry propanol (1.5 mL, excess) was added, followed by TfOH (1 μL), and the solution was stirred for 5 min. $NaHCO_3$ (~100 mg) was added, then the solution was diluted in EtOAc and washed with sat. aq. $NaHCO_3$, 10% aq. NaS_2O_3, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. FCC (5–10% EtOAc/CH_2Cl_2 gradient) gave **7** as a clear resin (21%); **TLC (10% EtOAc/CH_2Cl_2):** hR_f = 27 (**7**), 35 (**16**); **^{1}H NMR ($CDCl_3$):** δ 7.41–7.40 (2H, m), 6.37 (1H, dd, *J* = 1.6, 0.9 Hz), 5.55 (1H, dd, *J* = 11.7, 5.1 Hz), 4.77 (1H, d, *J* = 7.2 Hz), 4.76 (1H, d, *J* = 7.2 Hz), 4.17 (1H, dd, *J* = 12.1, 7.6 Hz), 3.71 (3H, s), 3.59 (1H, dt, *J* = 9.4, 6.6 Hz), 3.47 (1H, dt, *J* = 9.4, 6.6 Hz), 2.69 (1H, dd, *J* = 13.4, 3.5 Hz), 2.53 (1H, dd, *J* = 13.4, 5.2 Hz), 2.34 (1H, ddd, *J* = 13.5, 7.6, 3.5 Hz), 2.18 (1H, td, *J* = 13.2, 12.1 Hz), 2.15 (1H, dq, *J* = 13.5, 3.5 Hz), 2.06 (1H, br s), 2.05 (1H, dd, *J* = 11.7, 3.2 Hz), 1.77 (1H, m, Δν = 18.3 Hz), 1.71–1.46 (5H, m), 1.46 (3H, s), 1.10 (3H, s), 0.90 (3H, t, *J* = 7.4 Hz); **^{13}C NMR ($CDCl_3$):** δ 206.0, 171.8, 171.2, 143.7, 139.3, 125.3, 108.3, 94.4, 77.6, 72.0, 70.2, 64.2, 53.9, 51.9, 51.4, 43.4, 42.0, 38.1, 35.5, 32.6, 22.8, 18.1, 16.4, 15.2, 10.6; **HRMS(ESI):** $[M+H]^+$ *m/z* 463.2339 (calcd for $C_{25}H_{34}O_8$, 463.2332).

5.6. Salvinorin B butoxymethyl ether (8)

Procedure as for **7**, using butanol. FCC (3–6% EtOAc/CH_2Cl_2 gradient) gave **8** as a clear resin (24%); **TLC (5% EtOAc/CH_2Cl_2):** ***hR_f*** = 17 (**8**), 22 (**16**); **1H NMR ($CDCl_3$):** δ 7.41–7.39 (2H, m), 6.37 (1H, dd, *J* = 1.9, 1.0 Hz), 5.55 (1H, dd, *J* = 11.7, 5.1 Hz), 4.76 (1H, d, *J* = 7.1 Hz), 4.74 (1H, d, *J* = 7.1 Hz), 4.17 (1H, dd, *J* = 12.1, 7.4 Hz), 3.71 (3H, s), 3.63 (1H, dt, *J* = 9.4, 6.5 Hz), 3.51 (1H, dt, *J* = 9.4, 6.5 Hz), 2.69 (1H, dd, *J* = 13.3, 3.4 Hz), 2.53 (1H, dd, *J* = 13.3, 5.2 Hz), 2.34 (1H, ddd, *J* = 13.5, 7.5, 3.5 Hz), 2.18 (1H, td, *J* = 13.4, 12.2 Hz), 2.19–2.12 (1H, m), 2.06 (1H, br s), 2.05 (1H, dd, *J* = 11.5, 3.1 Hz), 1.78 (1H, m, Δν = 18.8 Hz), 1.71–1.45 (5H, m), 1.47 (3H, s), 1.34 (2H, m, Δν = 37 Hz), 1.11 (3H, s), 0.89 (3H, t, *J* = 7.3 Hz); **^{13}C NMR ($CDCl_3$):** δ 206.0, 171.8, 171.2, 143.7, 139.3, 125.2, 108.3, 94.4, 77.6, 72.0, 68.3, 64.2, 53.9, 51.9, 51.5, 43.5, 42.0, 38.2, 35.5, 32.5, 31.7, 19.3, 18.1, 16.4, 15.2, 13.8; **HRMS(ESI):** $[M+H]^+$ *m/z* 477.2506 (calcd for $C_{26}H_{36}O_8$, 477.2488).

5.7. Salvinorin B isopropoxymethyl ether (9)

Procedure as for **7**, using 2-propanol. FCC (0–10% EtOAc/CH_2Cl_2 gradient) gave **9** as a clear resin (18%); **TLC (10% EtOAc/CH_2Cl_2):** hR_f = 27(**9**), 41 (**16**); **1H NMR ($CDCl_3$):** δ 7.41–7.39 (2H, m), 6.37 (1H, dd, *J* = 1.6, 0.9 Hz), 5.54 (1H, dd, *J* = 11.7, 5.1 Hz), 4.83 (1H, d, *J* = 7.4 Hz), 4.74 (1H, d, *J* = 7.4 Hz), 4.21 (1H, dd, *J* = 12.2, 7.5 Hz), 3.93 (1H, sept, *J* = 6.1 Hz), 3.72 (3H, s), 2.70 (1H, dd, *J* = 13.5, 3.5 Hz), 2.53 (1H, dd, *J* = 13.2, 5.2 Hz), 2.33 (1H, ddd, *J* = 13.5, 7.5, 3.7 Hz), 2.18 (1H, dt, *J* = 13.4, 12.0 Hz), 2.15 (1H, dq, *J* = 13.5, 3.5 Hz), 2.07 (1H, br s), 2.05 (1H, dd, *J* = 11.4, 3.1 Hz), 1.78 (1H, m, Δν = 18.3 Hz), 1.71–1.45 (3H, m), 1.47 (3H, s), 1.18 (3H, d, *J* = 6.2 Hz), 1.13 (3H, d, *J* = 6.2 Hz), 1.10 (3H, s); **^{13}C NMR ($CDCl_3$):** δ 206.2, 171.9, 171.2, 143.7, 139.3, 125.3, 108.3, 92.2, 77.3, 72.0, 69.7, 64.2, 53.9, 51.9, 51.5, 43.4, 42.0, 38.2, 35.5, 32.5, 23.0, 22.0, 18.1, 16.4, 15.2; **HRMS(ESI):** $[M+NH_4]^+$ *m/z* 480.2618 (calcd for $C_{25}H_{34}O_8$, 480.2597).

5.8. Salvinorin B *tert*-butoxymethyl ether (10)

Procedure as for **7**, using 2-methyl- 2-propanol. FCC (0–5% EtOAc/CH_2Cl_2 gradient) gave **10** as a clear resin (40%); **TLC (10% EtOAc/CH_2Cl_2):** hR_f = 32 (**10**), 34 (**16**); **1H NMR ($CDCl_3$):** δ 7.41–7.39 (2H, m), 6.36 (1H, dd, *J* = 1.7, 1.0 Hz), 5.53 (1H, dd, *J* = 11.7, 5.0 Hz), 4.99 (1H, d, *J* = 8.2 Hz), 4.71 (1H, d, *J* = 8.2 Hz), 4.26 (1H, dd, *J* = 12.2, 7.3 Hz), 3.71 (3H, s), 2.70 (1H, dd, *J* = 13.3, 3.4 Hz), 2.51 (1H, dd, *J* = 13.3, 5.1 Hz), 2.32 (1H, ddd, *J* = 13.5, 7.3, 3.5 Hz), 2.20–2.10 (2H, m), 2.07 (1H, br s), 2.04 (1H, dd, *J* = 11.7, 3.1 Hz), 1.76 (1H, m, Δν = 17.9 Hz), 1.70–1.43 (3H, m), 1.45 (3H, s), 1.22 (9H, s), 1.09 (3H, s); **^{13}C NMR ($CDCl_3$):** δ 206.5, 171.9, 171.2, 143.7, 139.3, 125.2, 108.3, 88.7, 77.1, 75.0, 71.9, 64.1, 53.9, 51.9, 51.4, 43.4, 42.0, 38.1, 35.4, 32.5, 28.7, 18.1, 16.4, 15.2; **HRMS(ESI):** $[M+NH_4]^+$ *m/z* 494.2773 (calcd for $C_{26}H_{36}O_8$, 494.2754).

5.9. Salvinorin B 2-fluoroethoxymethyl ether (11)

Procedure as for **7**, using 2- fluoroethanol. FCC (0–5% EtOAc/CH_2Cl_2) gave **11** as a clear resin (18%). **TLC (10% EtOAc/CH_2Cl_2):** hR_f = 26 (**11**), 40 (**16**); **1H NMR ($CDCl_3$):** δ 7.42 (1H, dt, *J* = 1.6, 0.9 Hz), 7.40 (1H, t, *J* = 1.9 Hz), 6.38 (1H, dd, *J* = 1.9, 1.0 Hz), 5.55 (1H, dd, *J* = 11.6, 5.1 Hz), 4.82 (2H, s), 4.55 (2H, ~dt, *J* = 47.8, 4.1 Hz), 4.22 (1H, dd, *J* = 12.2, 7.5 Hz), 3.85 (2H, ~dt, *J* = 30.2, 4.1 Hz), 3.72 (3H, s), 2.70 (1H, dd, *J* = 13.2, 3.1 Hz), 2.53 (1H, dd, *J* = 13.1, 4.8 Hz), 2.35 (1H, ddd, *J* = 13.5, 7.5, 3.5 Hz), 2.18 (1H, dt, *J* = 13.2, 12.0 Hz), 2.18–2.12 (1H, m), 2.08 (1H, br s), 2.05 (1H, dd, *J* = 11.7, 2.9 Hz), 1.78 (1H, m, Δν = 18.2 Hz), 1.72–1.45 (3H, m), 1.47 (3H, s), 1.11 (3H, s); **^{13}C NMR ($CDCl_3$):** δ 205.8, 171.8, 171.2, 143.7, 139.3, 125.3, 108.3, 94.4, 82.7 (d, *J* = 168 Hz), 77.7, 72.0, 67.2 (d, *J* = 22 Hz), 64.3, 53.8, 51.9, 51.4, 43.4, 42.0, 38.2, 35.5, 32.4, 18.1, 16.4, 15.2; **^{19}F NMR ($CDCl_3$):** δ 5.6 (tt, *J* = 47.8, 30.3 Hz); **HRMS(ESI):** $[M+H]^+$ *m/z* 467.2096 (calcd for $C_{24}H_{31}FO_8$, 467.2081).

5.10. Salvinorin B 2,2,2-trifluoroethoxymethyl ether (12)

Procedure as for **7**, using 2,2,2-trifluoroethanol. FCC (0–5% EtOAc/CH_2Cl_2) gave **12** as a clear resin (11%). **TLC (10% EtOAc/CH_2Cl_2):** hR_f = 37 (**12**), 35 (**16**); **1H NMR ($CDCl_3$):** δ 7.42 (1H, dt, *J* = 1.8, 0.9 Hz), 7.40 (1H, t, *J* = 1.8 Hz), 6.38 (1H, dd, *J* = 1.9, 0.9 Hz), 5.55 (1H, dd, *J* = 11.6, 5.0 Hz), 4.84 (1H, d, *J* = 7.5 Hz), 4.82 (1H, d, *J* = 7.5 Hz), 4.17 (1H, dd, *J* = 12.2, 7.5 Hz), 4.05 (1H, dq, *J* = 12.0, 8.7 Hz), 3.95 (1H, dq, *J* = 12.0, 8.7 Hz), 3.72 (3H, s), 2.70 (1H, dd, *J* = 13.3, 3.5 Hz), 2.52 (1H, dd, *J* = 13.3, 5.1 Hz), 2.33 (1H, ddd, *J* = 13.6, 7.5, 3.7 Hz), 2.20 (1H, td, *J* = 13.3, 12.2 Hz), 2.16 (1H, dq, *J* = 13.6, 3.4 Hz), 2.08 (1H, br s), 2.05 (1H, dd, *J* = 11.9, 3.1 Hz), 1.79 (1H, m, Δν = 18.3 Hz), 1.72–1.49 (3H, m), 1.47 (3H, s), 1.10 (3H, s); **^{13}C NMR ($CDCl_3$):** δ 205.4, 171.6, 171.1, 143.7, 139.3, 125.3, 123.7 (q, *J* = 278 Hz), 108.3, 94.5, 78.5, 72.0, 64.9 (q, *J* = 34.6 Hz), 64.3, 53.7, 51.9, 51.4, 43.4, 42.0, 38.2, 35.5, 32.3, 18.1, 16.4, 15.2; **^{19}F NMR ($CDCl_3$):** δ −74.8 (t, *J* = 8.9 Hz); **HRMS(ESI):** $[M+H]^+$ *m/z* 503.1870 (calcd for $C_{24}H_{29}F_3O_8$, 503.1893).

5.11. Salvinorin B 2-methoxyethoxymethyl ether (13)

Procedure as for **7**, using 2- methoxyethanol. FCC (33–50% EtOAc/hexanes) gave **13** as a clear resin (15%). **TLC (10% EtOAc/CH_2Cl_2):** hR_f = 14 (**13**), 35 (**16**); **1H NMR ($CDCl_3$):** δ 7.42 (1H, dt, *J* = 1.6, 0.9 Hz), 7.40 (1H, t, *J* = 1.9 Hz), 6.38 (1H, dd, *J* = 1.8, 0.9 Hz), 5.54 (1H, dd, *J* = 11.7, 5.1 Hz), 4.82 (1H, d, *J* = 7.3 Hz), 4.80 (1H, d, *J* = 7.3 Hz), 4.22 (1H, dd, *J* = 12.2, 7.2

Hz), 3.79 (1H, m, Δν = 20.1 Hz), 3.71 (3H, s), 3.70 (1H, m, Δν = 20.1 Hz), 3.52 (2H, t, *J* = 4.5 Hz), 3.35 (3H, s), 2.68 (1H, dd, *J* = 13.5, 3.5 Hz), 2.52 (1H, dd, *J* = 13.3, 5.1 Hz), 2.36 (1H, ddd, *J* = 13.6, 7.2, 3.4 Hz), 2.18 (1H, td, *J* = 13.5, 12.3 Hz), 2.20–2.11 (1H, m), 2.06 (1H, br s), 2.04 (1H, dd, *J* = 11.6, 3.1 Hz), 1.78 (1H, m, Δν = 18.5 Hz), 1.71–1.44 (3H, m), 1.47 (3H, s), 1.11 (3H, s); **^{13}C NMR ($CDCl_3$):** δ 205.9, 171.8, 171.2, 143.7, 139.4, 125.3, 108.3, 94.6, 77.6, 71.9, 71.6, 67.3, 64.3, 59.0, 53.8, 51.9, 51.5, 43.5, 42.0, 38.2, 35.5, 32.5, 18.1, 16.4, 15.2; **HRMS(ESI):** $[M+NH_4]^+$ *m/z* 496.2528 (calcd for $C_{25}H_{34}O_9$, 496.2547).

5.12. Salvinorin B 2-(trimethylsilyl)ethoxymethyl ether (14)

Procedure as for **6**, using 2-(trimethylsilyl)ethyl chloromethyl ether for 23 h. FCC (33–50% EtOAc/hexanes) gave **12** as an amorphous white solid (53%). **TLC (50% EtOAc/hexanes):** hR_f = 72 (**14**), 24 (**2**); **^{1}H NMR ($CDCl_3$):** δ 7.41 (1H, dt, *J* = 1.6,0.9 Hz), 7.40 (1H, t, *J* = 1.7 Hz), 6.37 (1H, dd, *J* = 1.7, 0.9 Hz), 5.54 (1H, dd, *J* = 11.7, 5.0 Hz), 4.77 (1H, d, *J* = 7.2 Hz), 4.73 (1H, d, *J* = 7.2 Hz), 4.16 (1H, dd, *J* = 12.2, 7.5 Hz), 3.69 (1H, m, Δν = 26.8 Hz), 3.71 (3H, s), 3.59 (1H, m, Δν = 26.8 Hz), 2.69 (1H, dd, *J* = 13.5, 3.4 Hz), 2.52 (1H, dd, *J* = 13.3, 5.1 Hz), 2.33 (1H, ddd, *J* = 13.3, 7.2, 3.4 Hz), 2.18 (1H, td, *J* = 13.3, 12.2 Hz), 2.19–2.11 (1H, m), 2.06 (1H, br s), 2.05 (1H, dd, *J* = 11.3, 3.1 Hz), 1.77 (1H, m, Δν = 18.0 Hz), 1.71–1.48 (3H, m), 1.46 (3H, s), 1.10 (3H, s), 0.88 (2H, m, Δν = 16.8 Hz), 0.00 (9H, s); **^{13}C NMR ($CDCl_3$):** δ 206.0, 171.8, 171.2, 143.7, 139.3, 125.2, 108.3, 93.9, 77.7, 71.9, 65.7, 64.2, 53.9, 51.9, 51.4, 43.5, 41.9, 38.1, 35.5, 32.5, 18.1, 18.1, 16.4, 15.2, −1.4; **HRMS(ESI):** $[M+NH_4]^+$ *m/z* 538.2855 (calcd for $C_{27}H_{40}O_8Si$, 538.2836).

5.13. Salvinorin B benzyloxymethyl ether (15)

Procedure as for **6**, using $BnOCH_2Cl$ with NaI (1 eq) for 96 h. FCC (33% EtOAc/hexanes, then 5% MeOH/CH_2Cl_2) gave **15** as an amorphous white solid (34% [47% borsm]). **TLC (50% EtOAc/hexanes):** hR_f = 52 (**15**), 27 (**2**); **1H NMR ($CDCl_3$):** δ 7.41–7.40 (2H, m), 7.32– 7.28 (5H, m), 6.37 (1H, m, Δν = 2.8 Hz), 5.54 (1H, dd, *J* = 12.2, 5.3 Hz), 4.86 (1H, d, *J* = 7.2 Hz), 4.84 (1H, d, *J* = 7.2 Hz), 4.65 (2H, s), 4.19 (1H, dd, *J* = 12.0 ,7.5 Hz), 3.71 (3H, s), 2.66 (1H, dd, *J* = 13.0, 3.7 Hz), 2.50 (1H, dd, *J* = 13.2, 4.8 Hz), 2.33–2.11 (3H, m), 2.05 (1H, br s), 2.04 (1H, dd, *J* = 11.3, 2.9 Hz), 1.78 (1H, m, Δν = 18.6 Hz), 1.71–1.45 (3H, m), 1.47 (3H, s), 1.11 (3H, s); **^{13}C NMR ($CDCl_3$):** δ 205.8, 171.8, 171.2, 143.7, 139.4, 137.4, 128.5, 127.94, 127.90, 125.2, 108.4, 93.9, 77.9, 71.9, 70.1, 64.2, 53.8, 51.9, 51.5, 43.5, 42.0, 38.1, 35.5, 32.4, 18.1, 16.4, 15.2; **HRMS(ESI):** $[M+NH_4]^+$ *m/z* 528.2606 (calcd for $C_{29}H_{34}O_8$, 528.2597).

5.14. Salvinorin B methylthiomethyl ether (16)

Salvinorin B (**2**) (32.4 mg, 83 μmol) was dissolved in Me_2SO (1 mL). AcOH was added (1 mL), followed by Ac_2O (0.5 mL). The resulting white suspension was stirred at r.t. for 65 h, giving a clear yellow solution. Aq. NaOH (5.0 M, 5 mL) was added drop-wise, then the solution was diluted in EtOAc and washed with sat. aq. $NaHCO_3$ (× 3) and brine and dried ($MgSO_4$). Evaporation in vacuo gave **16** (33.7 mg, 90%) as an amorphous white solid of adequate purity for synthetic use. The receptor binding sample was purified by FCC (25% EtOAc/hexanes, stripped in 20% MeOH/CH_2Cl_2); **TLC (50% EtOAc/hexanes):** hR_f = 54 (**16**), 30 (**2**); **^{1}H NMR ($CDCl_3$):** δ 7.42 (1H, dt, *J* = 1.7, 0.8 Hz), 7.39 (1H, t, *J* = 1.7 Hz), 6.38 (1H, dd, *J* = 1.9, 0.9 Hz), 5.54 (1H, dd, *J* = 11.7, 5.1 Hz), 4.84 (1H, d, *J* = 11.9 Hz), 4.66 (1H, d, *J* = 11.9 Hz), 4.26 (1H, dd, *J* = 12.0, 7.4 Hz), 3.70 (3H, s), 2.72 (1H, dd, *J* = 13.4, 3.7 Hz), 2.54 (1H, dd, *J* = 13.4, 5.2 Hz), 2.28 (1H, ddd, *J* = 13.4, 7.5, 3.7 Hz), 2.19–2.10 (2H, m), 2.13 (3H, s), 2.09 (1H, br s), 2.05 (1H, dd, *J* = 12.2, 2.8 Hz), 1.76 (1H, m, Δν = 19 Hz), 1.70–1.48 (3H, m), 1.45 (3H, s), 1.10 (3H, s); **^{13}C NMR ($CDCl_3$):** δ 206.1, 171.8, 171.4, 143.7, 139.4, 125.4, 108.4, 74.5, 71.9, 64.4, 53.8, 51.8, 51.5, 43.6, 42.0, 38.2, 35.5, 32.3, 18.2, 16.4, 15.2, 13.7 (one signal not observed); **^{13}C NMR (C_5D_5N):** δ 207.0, 172.4, 171.4, 144.3, 140.4, 126.6, 109.4, 78.0, 74.8, 71.9, 63.5, 53.6, 51.6, 51.3, 43.4, 42.1, 38.3, 35.9, 33.0, 18.8, 16.5, 15.3, 13.7; **HRMS (ESI):** $[M+H]^+$ *m/z* 451.1792 (calcd for $C_{23}H_{30}O_7S$, 451.1790).

5.15. Salvinorin B fluoromethyl ether (17)

Procedure as for **7**, substituting Et_2NSF_3 (1.5 eq) for PrOH and omitting TfOH. FCC (66 – 100% Et_2O/hexanes, then 20% MeOH/CH_2Cl_2) gave **17** as an amorphous white solid (64% [81% based on recovered **2**]). A high-R_f byproduct was also recovered, along with **2**. These were pooled and briefly refluxed in MeOH/CH_2Cl_2/AcOH. Evaporation under reduced pressure and rinsing with minimal MeOH gave **2. TLC (Et_2O):** hR_f = 65 (byproduct), 54 (**16**), 48 (**17**), 32 (**2**); **1H NMR ($CDCl_3$):** δ 7.42 (1H, dt, *J* = 1.7, 0.9 Hz), 7.40 (1H, t, *J* = 1.8 Hz), 6.38 (1H, dd, *J* = 1.8, 0.9 Hz), 5.55 (1H, dd, *J* = 11.7, 5.1 Hz), 5.40 (1H, dd, *J* = 53.2, 3.0 Hz), 5.26 (1H, dd, *J* = 58.7, 3.0 Hz), 4.24 (1H, dd, *J* = 12.1, 7.6 Hz), 3.72 (3H, s), 2.70 (1H, dd, *J* = 13.8, 3.4 Hz), 2.53 (1H, dd, *J* = 13.3, 5.2 Hz), 2.42 (1H, ddd, *J* = 13.5, 7.4, 3.5 Hz), 2.24 (1H, td, *J* = 13.5, 12.3 Hz), 2.16 (1H, dq, J = 13.5, 3.2 Hz), 2.08 (1H, br s), 2.05 (1H, dd, J = 11.0, 3.2 Hz), 1.79 (1H, m, Δν = 18.3 Hz), 1.71–1.42 (3H, m), 1.46 (3H, s), 1.12 (3H, s); **^{13}C NMR ($CDCl_3$):** δ 204.5, 171.5, 171.0, 143.8, 139.4, 125.2, 108.3, 102.4 (d, *J* = 214 Hz), 79.8, 71.9, 64.3, 53.6, 51.9, 51.4, 43.5, 42.0, 38.1, 35.5, 32.3, 18.1, 16.4, 15.2; **^{19}F NMR ($CDCl_3$):** δ −152.2 (dd, *J* = 58.7, 53.8 Hz); **HRMS(ESI):** $[M+H]^+$ *m/z* 423.1813 (calcd for $C_{22}H_{27}FO_7$, 423.1819).

5.16. Salvinorin B 1-ethoxyethyl ether (18)

Salvinorin B (**2**) (49.1 mg, 126 μmol) was dissolved in dry CH_2Cl_2 (1.5 mL) under Ar and stirred at 0 °C. Ethoxyethene (100 μL, 1.04 mmol) and a speck of *p*-TsOH (≪ 1 mg, catalytic) were added. The resulting suspension was removed from the icebath and stirred at room temperature for 10 min, when it had clarified and turned yellow. TLC (50% EtOAc/hexanes) showed minimal starting material. The solution was diluted in EtOAc and washed with sat. aq. $NaHCO_3$ (× 3) and dried ($MgSO_4$). Evaporation under reduced pressure and repeated FCC (25– 50% EtOAc/hexanes, then 20% MeOH/CH_2Cl_2) gave **18a** as an amorphous white solid (20.6 mg, 36%); **TLC (50% EtOAc/hexanes):** hR_f = 48 (**18a**), 43 (**18b**), 30 (**2**); **^{1}H NMR (C_6D_6):** δ 7.10 (1H, dt, *J* = 1.6, 0.9 Hz), 7.05 (1H, t, *J* = 1.7 Hz), 6.14 (1H, dd, *J* = 1.9, 0.9 Hz), 5.18 (1H, dd, *J* = 11.7, 5.0 Hz), 4.94 (1H, q, *J* = 5.4 Hz), 4.00 (1H, m, Δν = 19 Hz), 3.44 (1H, dq, *J* = 9.2, 7.1 Hz), 3.32 (1H, dq, *J* = 9.2, 7.1 Hz), 3.29 (3H, s), 2.35–2.09 (5H, m), 1.54–1.43 (3H, m), 1.40 (3H, d, *J* = 5.4 Hz), 1.30 (1H, br s), 1.27 (3H, s), 1.24–1.05 (2H, m), 1.07 (3H, t, *J* = 7.1 Hz), 0.89 (3H, s); **^{13}C NMR (C_6D_6):** δ 206.3, 171.7, 170.1, 143.7, 139.4, 126.5, 108.7, 99.2, 76.9, 71.5, 63.6, 58.4, 53.7, 51.3, 51.1, 43.6, 41.7, 38.1, 35.5, 33.2, 19.8, 18.6, 16.2, 15.7, 15.1; **HRMS(ESI):** $[M+H]^+$ *m/z* 463.2318 (calcd for $C_{25}H_{34}O_8$, 463.2332).

Mixed fractions were pooled with other runs; further chromatography gave **18b** as an amorphous white solid (16%); **^{1}H NMR (C_6D_6):** δ 7.11 (1H, dt, *J* = 1.7, 0.9 Hz), 7.05 (1H, t, *J* = 1.7 Hz), 6.16 (1H, dd, *J* = 1.9, 0.9 Hz), 5.18 (1H, dd, *J* = 11.7, 5.0 Hz), 4.73 (1H, q, *J* = 5.4 Hz), 3.83 (1H, m, Δν = 19 Hz), 3.64 (1H, dq, *J* = 9.4, 7.1 Hz), 3.52 (1H, dq, *J* = 9.4, 7.1 Hz), 3.31 (3H, s), 2.36–2.22 (3H, m), 2.20–2.07 (2H, m), 1.59–1.41 (3H, m), 1.32 (1H, br s), 1.29 (3H, s), 1.25–1.04 (2H, m), 1.21 (3H, d, *J* = 5.4 Hz), 1.06 (3H, t, *J* = 7.1 Hz), 0.91 (3H, s); **^{13}C NMR (C_6D_6):** δ 205.5, 171.8, 170.1, 143.7, 139.4, 126.6, 108.6, 98.6, 75.3, 71.5, 63.8, 60.9, 53.8, 51.3, 51.1, 43.5, 41.8, 38.2, 35.5, 33.4, 20.0, 18.7, 16.1, 15.5, 15.1; **HRMS(ESI):** $[M+H]^+$ *m/z* 463.2342 (calcd for $C_{25}H_{34}O_8$, 463.2332).

5.17. Salvinorin B 2-methoxy-2-propyl ether (19)

Salvinorin B (**2**) (40.4 mg, 103 μmol) was dissolved in dry CH_2Cl_2 (1 mL) under Ar. Pyridinium *p*-toluenesulfonate in dry CH_2Cl_2 (10 mM) was added (1 mL, 10 μmol). 2-Methoxypropene (100 μL, 1.04 mmol) was added, and the solution was stirred at room temperature for 35 minutes, monitored by TLC (50% EtOAc/hexanes). The reaction mixture was quenched with excess NEt_3 (200 μL), loaded directly onto silica gel and purified by FCC (0.5% NEt_3/10 – 50% EtOAc/hexanes, then 20% MeOH/CH_2Cl_2) to give **19** as an amorphous white solid (13.7 mg, 31%); **TLC (50% EtOAc/hexanes):** hR_f = 59 (byproduct), 43 (**19**), 30 (**2**); **1H NMR ($CDCl_3$):** δ 7.40–7.39 (2H, m), 6.36 (1H, dd, *J* = 1.6, 0.9), 5.53 (1H, dd, *J* = 11.6, 5.1 Hz), 4.22 (1H, ~dd, *J* = 20.9, 8.4 Hz), 3.71 (3H, s), 3.21 (3H, s), 2.70 (1H, ~dd, *J* = 10.9, 5.6 Hz), 2.46 (1H, dd, *J* = 13.2, 5.1 Hz), 2.26–2.15 (2H, m), 2.14 (1H, dq, *J* = 13.5, 3.5 Hz), 2.09 (1H, br s), 2.04 (1H, dd, *J* = 11.3, 2.7 Hz), 1.79 (1H, m, Δν = 18.5 Hz), 1.71–1.45 (3H, m), 1.47 (3H, s), 1.40 (3H, s), 1.27 (3H, s), 1.09 (3H, s); **^{13}C NMR ($CDCl_3$):** δ 206.6, 171.9, 171.2, 143.7, 139.4, 125.3, 108.3, 101.3, 73.5, 71.8, 64.5, 54.2, 51.8, 51.4, 49.4, 43.3, 42.1, 38.3, 35.4, 33.8, 25.0, 24.7, 18.1, 16.2, 15.1; **HRMS(ESI):** $[M+H]^+$ *m/z* 463.2342 (calcd for $C_{25}H_{34}O_8$, 463.2332).

5.18. Salvinorin B tetrahydropyran-2-yl ether (20)

Procedure as for **18**, using 3,4- dihydro-2*H*-pyran. Repeated FCC (33–50% EtOAc/hexanes, then 20% MeOH/CH_2Cl_2) gave **20** as a clear resin (28.6 mg, 47%); **TLC (50% EtOAc/ hexanes):** hR_f = 58 (**20**), 52 (epimeric acetal), 35 (**2**); **^1H NMR ($CDCl_3$, filtered through basic Al_2O_3):** δ 7.43–7.39 (2H, m), 6.38 (1H, dd, *J* = 1.9, 0.9 Hz), 5.53 (1H, dd, *J* = 11.9, 5.3 Hz), 4.74 (1H, t, *J* = 3.0 Hz), 4.25 (1H, dd, *J* = 12.2, 7.6 Hz), 3.81 (1H, ddd, *J* = 11.6, 9.0, 3.0 Hz), 3.71 (3H, s), 3.50 (1H, dt, *J* = 11.1, 4.5 Hz), 2.71 (1H, dd, *J* = 13.2, 3.7 Hz), 2.54 (1H, dd, *J* = 13.2, 5.1 Hz), 2.36 (1H, ddd, *J* = 13.5, 7.6, 3.8 Hz), 2.24 (1H, td, *J* = 13.4, 12.2 Hz), 2.15 (1H, dq, *J* = 13.2, 3.2 Hz), 2.06 (1H, br s), 2.05 (1H, dd, *J* = 13.3, 3.2 Hz), 1.88–1.41 (10H, m), 1.46 (3H, s), 1.12 (3H, s); **^1H NMR (C_6D_6):** δ 7.05–7.04 (2H, m), 6.11 (1H, q, *J* = 1.5 Hz), 5.16 (1H, dd, *J* = 11.8, 5.2 Hz), 5.00 (1H, t, *J* = 2.9 Hz), 4.06 (1H, m, Δν = 18 Hz), 3.70 (1H, td, *J* = 11.1, 3.0 Hz), 3.36 (1H, m, Δν = 20 Hz), 3.30 (3H, s), 2.43–2.23 (4H, m), 2.11 (1H, m, Δν = 26 Hz), 1.93 (1H, m, Δν = 24 Hz), 1.80–1.62 (2H, m), 1.49–1.00 (8H, m), 1.27 (3H, s), 1.02 (1H, td, *J* = 7.2, 1.5 Hz), 0.90 (3H, s); **^{13}C NMR (C_6D_6):** δ 206.3, 171.8, 170.1, 143.6, 139.4, 126.5, 108.7, 97.8, 76.9, 71.5, 63.7, 61.5, 53.7, 51.3, 51.1, 43.7, 41.6, 38.1, 35.5, 33.1, 30.3, 25.8, 18.8, 18.6, 16.2, 15.1; **HRMS(ESI):** $[M+H]^+$ *m/z* 475.2342 (calcd for $C_{26}H_{34}O_8$, 475.2332).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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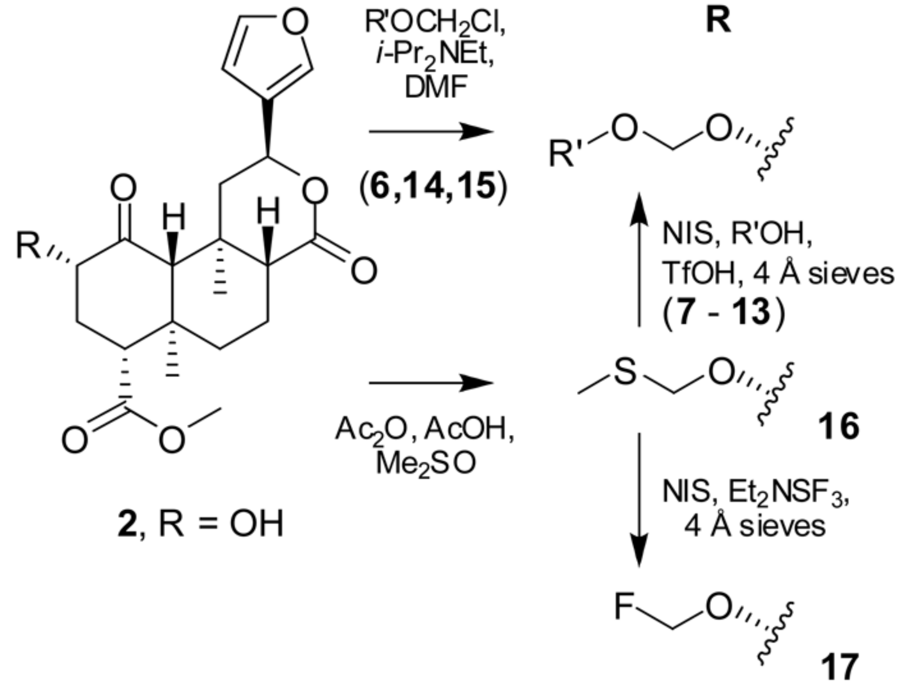
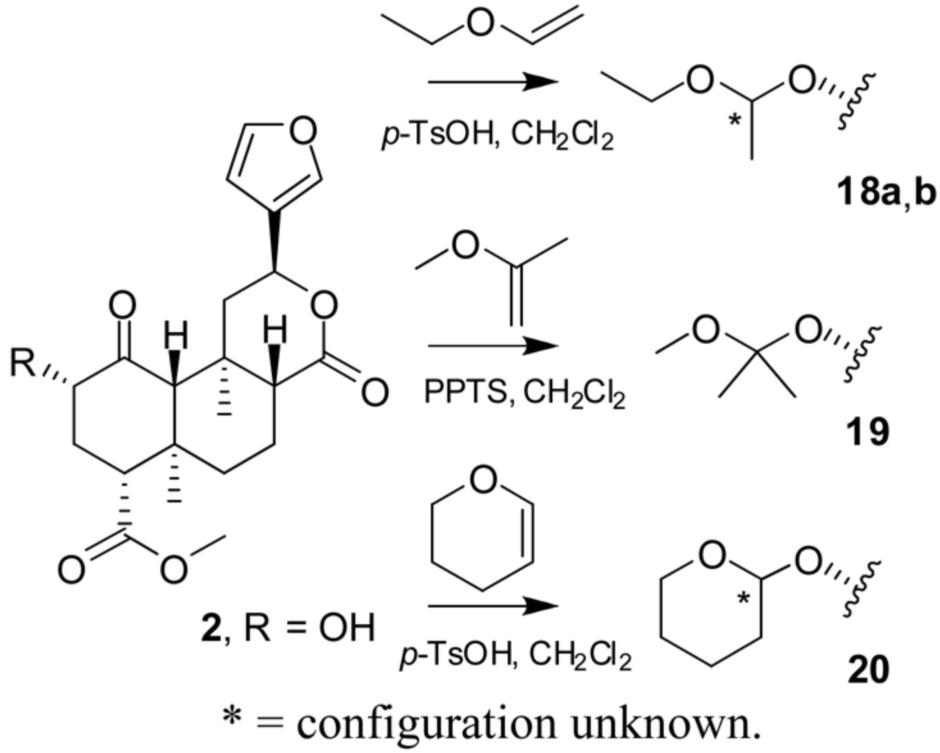


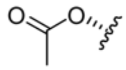
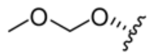
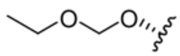
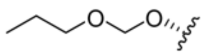
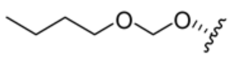
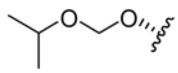
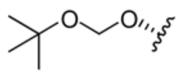
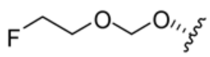
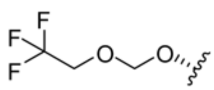
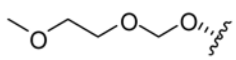
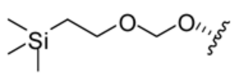
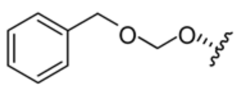
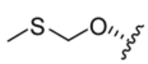
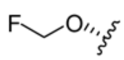
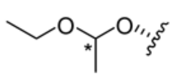
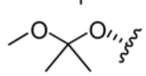
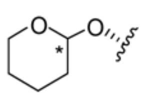
Scheme 1.
Synthesis of alkoxymethyl ethers and fluoromethyl ether.



Scheme 2.
Synthesis of other alkoxyalkyl ethers.

Table 1

Affinities (K_i) and potencies (EC_{50}) at the κ opioid receptor.

	R	K_i ± SEM (nM)[a,b]	EC_{50} ± SEM (nM)[b,c]
1		2.4 ± 0.4	1.8 ± 0.5
5		0.60 ± 0.07	0.40 ± 0.04
6		0.32 ± 0.02	0.14 ± 0.01
7		2.2 ± 0.6	5.2 ± 0.4
8		5.3 ± 1.7	20 ± 3.5
9		1.6 ± 0.5	4.2 ± 0.7
10		35 ± 15	108 ± 18
11		1.9 ± 0.5	3.8 ± 0.3
12		31 ± 8	75 ± 7
13		141 ± 29	320 ± 13
14		> 1,000	1,660 ± 60
15		147 ± 26	274 ± 16
16		13 ± 3	31 ± 8
17		50 ± 9	26 ± 6
18a **18b**		11 ± 1 6.6 ± 0.3	10 ± 1 5.7 ± 0.7
19		72 ± 13	72 ± 5
20		4.0 ± 0.4	2.8 ± 0.3
	U50,488H	2.2 ± 0.3	1.4 ± 0.3

[a] Inhibition of $[^3H]$diprenorphine binding to CHO-hKOR.

[b] Mean of three independent experiments performed in duplicate.

[c] Enhancement of $[^{35}S]$GTPγS binding to CHO-hKOR. All compounds were full agonists (E_{max} = 81–106% relative to U50,488H).

* configuration unknown.