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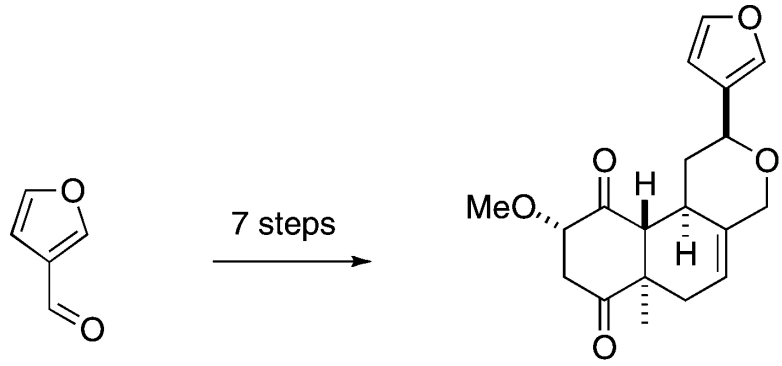

3a

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JOC*Note*

Total Synthesis of 20-Norsalvinorin A. 1. Preparation of a Key Intermediate

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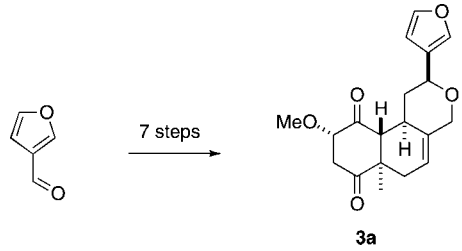


The key tricylic intermediate **3a**, for the total synthesis of the C_{20}-nor analogue of salvinorin A, was prepared in seven steps from 3-furaldehyde. Key steps involved a highly regio- and diastereoselective Lewis acid assisted Diels−Alder reaction followed by base-promoted epimerization and a completely stereoselective conjugate reduction.

Salvinorin A (**1**) is a highly potent and selective κ-opioid receptor (KOR) agonist, both in vivo and in vitro, with no significant affinity for any other opioid receptor subtype.[1] It was originally isolated in 1982 from the perennial herb *Salvia divinorum* by Ortega[2] and independently by Valdés.[3] Two total syntheses of salvinorin A have been reported. One by Evans[4] in 29 steps via a transannular Michael reaction cascade and the other by Hagiwara[5] in 20 steps from enantiomerically pure Wieland−Miescher ketone. In addition, partial syntheses have been disclosed by Hügel[6] and Forsyth.[7]

Because of the remarkable affinity for the KOR, the functional groups of salvinorin A have been extensively modified, and subsequent SAR studies have begun to clarify the pharmacophore. The rapidly expanding library of salvinorin A analogues includes modifications at the C_1, C_2, C_4, C_{17}, and C_8 position (Figure 1).[8] To date no studies have evaluated the importance, if any, of the C_{20}-methyl group. From its location on the salvinorin skeleton modification of C_{20} is clearly very difficult. Hence we decided to prepare the C_{20}-nor analogue of salvinorin A through total synthesis. Herein we describe a short, expeditious, synthesis of key intermediate **3a** (Scheme 1).

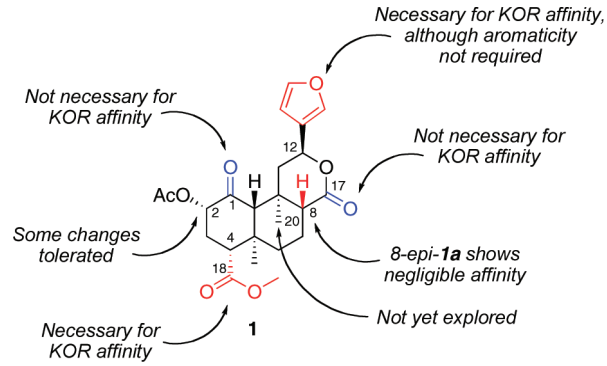
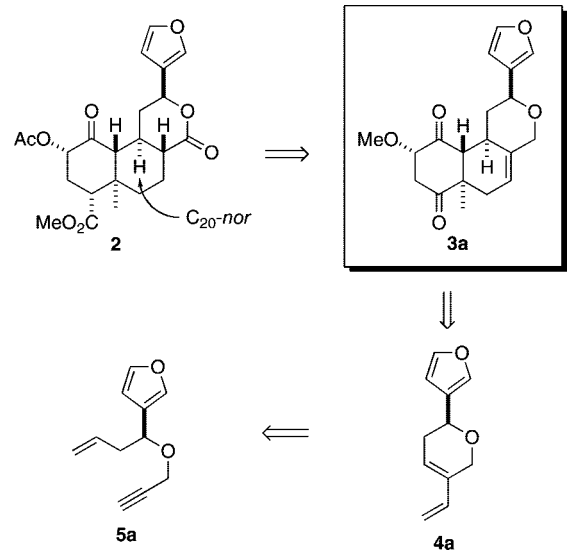


FIGURE 1. Summary of the outcomes of SAR studies on salvinorin A (**1**).

SCHEME 1. Retrosynthetic Analysis of 20-Norsalvinorin Analogue Including the Target Intermediate 3a



From the retrosynthesis shown in Scheme 1, the key step is an *endo-syn* selective intermolecular Diels−Alder addition of a semicyclic dihydropyran-based diene (**4a**). It is envisaged that the C_{18}-methoxycarbonyl group will be introduced via Pd-catalyzed carbonylation of the enoltriflate of **3a**.[9] A sequence of conjugate reduction of the unsaturated ester followed by allylic oxidation and Evans[4] conjugate reduction of the resulting unsaturated lactone would provide the 20-norsalvinorin A skeleton. Demethylation followed by acetylation completes the synthesis of **2**.

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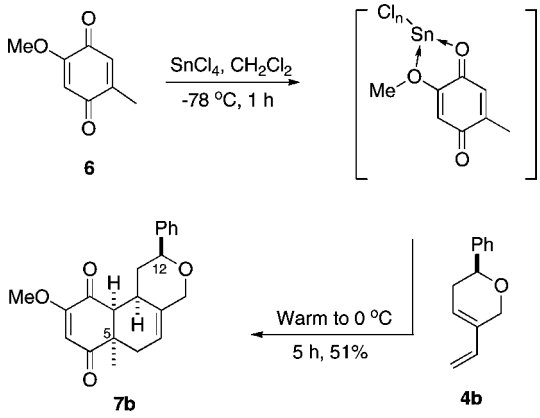
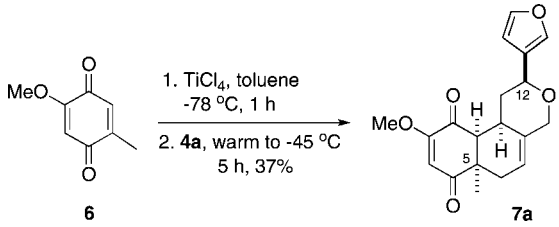
SCHEME 2. Stannic Chloride Mediated Diels–Alder Reactions of Diene 4b with 2-Methoxy-5-methyl-1,4-benzoquinone (6)



SCHEME 3. Titanium-tetrachloride Mediated Diels–Alder Reactions of Diene 4a with 2-Methoxy-5-methyl-1,4-benzoquinone (6)

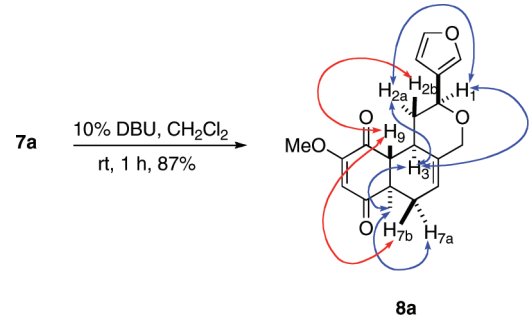


Model studies of the Diels–Alder reaction were carried out with a phenyl-substituted diene **4b** (prepared in three steps[10] from benzaldehyde) with 2-methoxy-5-methyl-1,4-benzoquinone[11] (**6**). By analogy with the work of Carreño, it was anticipated that a mixture of *endo-anti* and *endo-syn* adducts would be obtained.[12] However, unlike Carreño's dienophiles, which reacted completely after 16 h at room temperature, no reaction was observed between **4b** and **6** after 3 days at 80 °C. In order to increase the reactivity of **4b**, we turned to precomplexation of the methoxyquinone with metal salts.

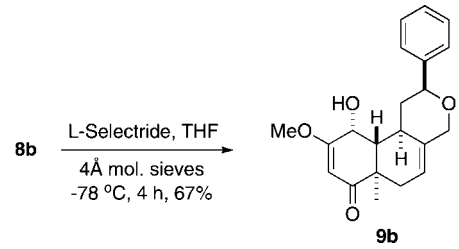
Thus, employing the method of Reusch,[13] **4b** was added to a precomplexed mixture of **6** and $SnCl_4$ at low temperature. Reaction was found to commence upon warming to approximately −45 °C. After 4 h at this temperature, the reaction was quenched, and an inseparable mixture of two products was obtained. However, allowing the reaction mixture to warm to 0 °C produced the desired adduct **7b** in 51% yield (Scheme 2). Apparently at this higher temperature the second product either is converted to **7b** via a retro-Diels–Alder pathway or simply decomposes under the conditions.

Diene **4a**, prepared according to Snapper's protocol in three steps from 3-furaldehyde,[10] was then added to **6** under conditions similar to those just described for **4b** (Scheme 3). Only decomposition was observed when the reaction was warmed to 0 °C. At lower temperatures very poor conversion was obtained with a highest yield of only ∼20%. Switching to the use of $TiCl_4$ gave decomposition at −45 °C. Running the reaction at

SCHEME 4. Epimerization of Adduct 7a To Adjust the Stereochemistry at C_{10}



SCHEME 5. Attempted Conjugate Reduction of Epimerized Adduct 8b



−78 °C in dichloromethane gave a 1:1 mixture of two adducts. Changing the solvent to toluene gave no reaction at −78 °C. However, at −45 °C a 1:1 ratio of adducts was again obtained, providing the desired *endo-syn* product **7a** in 37% isolated yield.

Although yields were modest (37% and 51% for **7a** and **7b**, respectively), the major product in each case was formed with full regiocontrol with the three newly created stereogenic centers (at C_5, C_9, and C_{10}) in the same orientation as the natural product. Significantly, the relative stereochemistry between C_5 and C_{12} in **7a** is also correct for the natural product. Interestingly a small amount (∼10%) of **8a** (vide infra) was also present in the product. Thus, some epimerization of the adduct had occurred after cycloaddition.

With **7a** and **7b** in hand, it remained for us to adjust the relative stereochemistry at C_{10} and introduce the correct stereochemistry at C_2 (Scheme 4). Thus treatment of **7a** with DBU at room temperature in dichloromethane for 1 h gave smooth conversion to a single product, **8a** (adduct **7b** behaved similarly, cleanly epimerizing to **8b**).

A variety of conditions were explored in order to effect reduction of **8a** and **8b**. All attempts to achieve this transformation with copper-[14] and zinc-based[15] reagents led to mixtures of 1,2-reduction products. In the case of L-Selectride[16] smooth conversion to a single 1,2-reduction product, **9b**, was observed (Scheme 5).

Finally, alkaline dithionite was employed as the reducing system.[17] Unlike previous reductions, this led to exclusive conjugate reduction installing the correct relative stereochemistry at C_2 without loss of OMe. Similar results were obtained for both **8a** and **8b** (Scheme 6). A crystal structure for **3b** was obtained that confirmed our assignments of relative stereochemistry (see Supporting Information).

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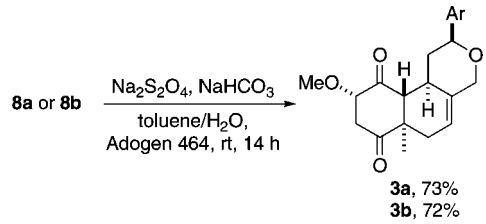
SCHEME 6. Successful Conjugate Reduction of Epimerized Adducts 8a and 8b



With a short route to intermediate **3a** now developed, studies directed toward the synthesis of **2** and evaluation of its KOR selectivity are underway in our laboratories and will be published in due course.

Experimental Section

***rac*-(2*S*,6a*R*,10a*S*,10b*R*)-9-Methoxy-6a-methyl-2-phenyl-6,6a,10a,10b-tetrahydro-1*H*-benzo[*f*]isochromene-7,10(2*H*,4*H*)-dione (7b).** To a stirring solution of 2-methoxy-5-methyl-1,4-benzoquinone (**6**) (2.50 g, 16.43 mmol) in dry CH_2Cl_2 (120 mL) under an atmosphere of argon was added a 1.0 M solution of $SnCl_4$ in CH_2Cl_2 (13.1 mL, 13.1 mmol), dropwise at −78 °C. Stirring was continued at this temperature for 1 h, after which a solution of diene **4b** (1.84 g, 9.86 mmol) in CH_2Cl_2 (30 mL) was added slowly. The reaction was stirred at −78 °C for 15 min and then at 0 °C for 5 h. Quenching of the reaction was done at −78 °C by the addition of brine (20 mL), the mixture was warmed to room temperature, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic layers were washed with brine (70 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to yield a brown residue. This residue was subsequently stirred with aqueous sodium bisulfite ($NaHSO_3$) solution for 1 h and then extracted with CH_2Cl_2. The combined organic layers were washed and dried in the same manner as above, and the resulting brown foam was purified by flash chromatography (2:3 EtOAc/hexanes) to afford **7b** (1.70 g, 51%) as a pale orange solid. Mp 144−146 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23−7.29 (5H, m), 5.80 (1H, s), 5.61 (1H, d, J = 1.4 Hz), 4.39 (1H, dd, J = 11.0, 2.0 Hz), 4.31 (1H, d, J = 12.4 Hz), 4.11 (1H, dq, J = 12.5, 2.8, 1.4 Hz), 3.71 (3H, s), 3.17 (1H, d, J = 7.2 Hz), 2.89 (1H, m), 2.81 (1H, ddt, J = 17.9, 4.7, 1.6 Hz), 1.95 (1H, q, J = 23.6, 12.6 Hz), 1.81 (1H, dq, J = 17.9, 5.6, 2.3 Hz), 1.58 (1H, ddd, J = 12.5, 4.2, 2.0 Hz), 1.34 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8, 195.7, 162.3, 141.9, 133.5, 128.5, 127.7, 126.1, 119.4, 109.6, 80.7, 72.7, 56.6, 55.7, 47.7, 38.5, 36.9, 31.8, 26.9. IR (neat): ν 3063w, 3030w, 2937m, 2844m, 1708m, 1662s, 1606s cm^{-1}. ESI-MS: m/z 361.2 $[M + Na]^+$. ESI-HRMS calcd for $[M + Na]^+$ ($C_{21}H_{22}NaO_4$): m/z 361.1416, found 361.1405. Anal. Calcd for $C_{21}H_{22}O_4$: C 74.54, H 6.55. Found: C 74.15, H 6.52.

***rac*-(2*S*,6a*R*,10a*S*,10b*R*)-2-(Furan-3-yl)-9-methoxy-6a-methyl-6,6a,10a,10b-tetrahydro-1*H*-benzo[*f*]isochromene-7,10(2*H*,4*H*)-dione (7a).** To a stirring solution of 2-methoxy-5-methyl-1,4-benzoquinone (**6**) (860 mg, 5.65 mmol) in dry toluene (45 mL) under an atmosphere of argon was added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (4.52 mL, 4.52 mmol) dropwise at −78 °C. Stirring was continued at this temperature for 1 h, after which a solution of diene **4a** (598 mg, 3.39 mmol) in toluene (5 mL) was added slowly. The reaction was stirred at −78 °C for 15 min and then at −45 °C for 5 h. Quenching of the reaction was done at −78 °C by the addition of brine (10 mL), the mixture was warmed to room temperature, and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 15 mL), and the combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (2:3 EtOAc/hexanes) to afford **7a** (411 mg, 37%) as a yellow gum. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (1H, t, J = 1.6 Hz), 7.32 (1H, m), 6.32 (1H, m), 5.83 (1H, s), 5.58 (1H, m), 4.39 (1H, dd, J = 11.0, 1.7 Hz), 4.24 (1H, d, J = 12.5 Hz), 4.08 (1H, dm, J = 12.5), 3.76 (3H, s), 3.16 (1H, d, J = 6.7 Hz), 2.74−2.86 (2H, m), 2.04 (1H, q, J = 23.7, 12.4 Hz), 1.80 (1H, dq, J = 17.8, 5.6, 2.8 Hz), 1.57 (1H, ddd, J = 12.4 Hz, 4.3, 2.0 Hz), 1.33 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.7, 195.6, 162.4, 143.2, 139.1, 133.3, 126.6, 119.4, 109.5, 108.7, 73.4, 72.5, 56.6, 55.6, 47.8, 37.1, 36.3, 31.9, 26.5. IR (neat): ν 3065w, 2945m, 2840m, 1711m, 1661s, 1609s cm^{-1}. ESI-MS: m/z 351.2 $[M + Na]^+$. ESI-HRMS Calcd for $[M + Na]^+$ ($C_{19}H_{20}NaO_5$): m/z 351.1208, found 351.1205.

***rac*-(2*S*,6a*R*,10a*R*,10b*R*)-2-(Furan-3-yl)-9-methoxy-6a-methyl-6,6a,10a,10b-tetrahydro-1*H*-benzo[*f*]isochromene-7,10(2*H*,4*H*)-dione (8a).** To a stirring solution of **7a** (63 mg, 0.19 mmol) in dry CH_2Cl_2 (3 mL) under an atmosphere of argon was added DBU (2.8 μL, 0.019 mmol), and the resulting solution was stirred for 1 h at room temperature. The solvent was evaporated, and the brown residue was immediately purified on a short plug of silica gel (2:3 EtOAc/hexanes) to yield **8a** (55 mg, 87%) as an yellow gum. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (1H, m), 7.35 (1H, t, J = 1.8 Hz), 6.37 (1H, m), 5.81 (1H, s), 5.62 (1H, m), 4.63 (1H, dd, J = 11.3, 1.6 Hz), 4.25 (1H, d, J = 12.5 Hz), 4.16 (1H, dm, J = 12.4 Hz), 3.79 (3H, s), 2.95 (1H, m), 2.78 (1H, d, J = 9.8 Hz), 2.57 (1H, ddd, J = 12.7, 4.6, 2.0 Hz), 2.51 (1H, dm, J = 20.0 Hz), 2.28 (1H, ddt, J = 18.5, 5.7, 2.0 Hz), 1.30 (1H, dt, J = 12.7, 11.4 Hz), 1.14 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.4, 194.7, 163.1, 143.2, 139.1, 132.8, 126.7, 119.3, 109.1, 108.7, 72.4, 72.4, 56.5, 56.4, 48.2, 39.8, 33.1, 32.4, 21.1. IR (neat): ν 2962m, 2844m, 1711m, 1661s, 1605s cm^{-1}. ESI-HRMS calcd for $[M + Na]^+$ ($C_{19}H_{20}NaO_5$): m/z 351.1208, found 351.1215.

***rac*-(2*S*,6a*R*,9*S*10a*R*,10b*R*)-2-(Furan-3-yl)-9-methoxy-6a-methyl-6,6a,8,9,10a,10b-hexahydro-1*H*-benzo[*f*]isochromene-7,10(2*H*,4*H*)-dione (3a).** To a stirring solution of **8a** (45 mg, 0.14 mmol) in toluene (4.5 mL) was added Adogen 464 (20 μL) followed by a solution containing $NaHCO_3$ (184 mg, 42.7 mmol) and $Na_2S_2O_4$ (tech, ∼85%) (280 mg, 26.7 mmol) in water (6 mL). The biphasic system was stirred vigorously at room temperature under an atmosphere of nitrogen for 7 h, after which a second portion of $Na_2S_2O_4$ (tech, ∼85%) (56 mg, 0.274 mmol) was added. Upon stirring for another 7 h, the layers were separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting yellow residue was purified by flash chromatography (2:3 EtOAc/hexanes) to yield **3a** (33 mg, 73%) as a white solid. Mp 142−145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (1H, m), 7.35 (1H, t, J = 2.1 Hz), 6.37 (1H, m), 5.56 (1H, m), 4.60 (1H, dd, J = 11.2, 1.8 Hz), 4.25 (1H, d, J = 12.6 Hz), 4.15 (1H, dm, J = 12.6 Hz), 4.04 (1H, ddd, J = 12.0, 7.6, 0.9 Hz), 3.47 (3H, s), 3.09 (1H, dd, J = 14.8, 7.6 Hz), 3.02 (1H, m), 2.95 (1H, dd, J = 14.8, 12.0 Hz), 2.58 (1H, dm, J = 18.4 Hz), 2.44 (1H, d, J = 9.9 Hz), 2.24 (1H, ddd, J = 12.5, 4.8, 2.0 Hz), 2.05 (1H, ddt, J = 18.4, 5.7, 2.0 Hz), 1.19 (1H, q, J = 24.0, 11.5 Hz) 1.03 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.7, 205.8, 143.2, 139.1, 132.8, 126.7, 118.9, 108.7, 80.9, 72.4, 72.3, 58.5, 52.9, 49.2, 44.8, 39.5, 33.0, 31.3, 19.1. IR (neat): ν 2930m, 2907m, 1717s, 1684m, 1654w, 1636w, 1559m cm^{-1}.

Acknowledgment. Y.B. and P.P. thank the ARC Centre for Green Chemistry for partial funding of this research.

Supporting Information Available: General experimental, experimental procedures, and characterization data for compounds **3b**, **4a**, **4b**, **5a**, **5b**, **8b**, and **9b** and ^{1}H NMR and ^{13}C NMR spectra for all new compounds, as well as the crystal structure of **3b** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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