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1,3-Diaxially Substituted *trans*-Decalins: Potential Nonsteroidal Human Progesterone Receptor Inhibitors

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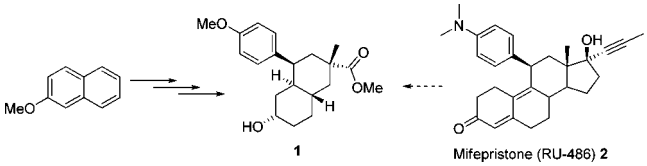

On the basis of molecular modeling and QSAR analysis of the known human progesterone receptor (hPR) inhibitor Mifepristone (RU-486) and other hPR ligands, a new class of potential nonsteroidal hPR inhibitors was designed. The parent racemic compound **1** was synthesized through an efficient 13-step synthetic pathway. The key constructive steps are a stereoselective epoxide ring opening and the reductive Heck cyclization to form the main framework of (±)-**1**. The current established flexible synthetic route allows for further chemical diversification.

The steroidal hormone progesterone plays a vital role in maintaining pregnancy in animals. Disrupting or blocking progesterone's activity could serve as a viable method for the management of human fertility. To date, hormone replacement therapy has been an important tool in birth control and in the treatment of hormone-dependent diseases. Among the known human progesterone receptor (hPR) antagonists, Mifepristone (RU-486) **2** is a successful example of their potential use as birth control agents. This drug also has potential as an adjuvant treatment tool in the management of hormone-dependent tumors and disorders of the female reproductive system that are refractory to chemotherapy.[1,2] All currently available anti-progestins are steroidal compounds. One of the difficulties in using steroid-like agents is that these highly hydrophobic compounds usually exhibit poor bioavailability. Thus the development of nonsteroidal hPR antagonists is a goal worth pursuing.

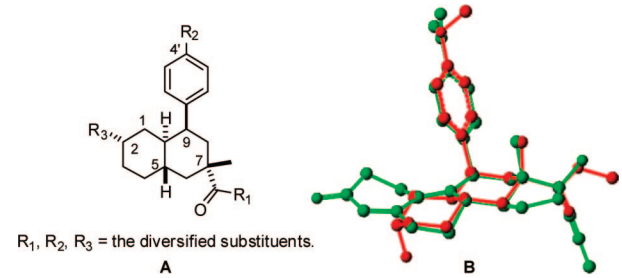

FIGURE 1. The basic framework of the RU-486 analogues; **B**. Overlay of a representative compound **1** (red) with **2** (green).

With RU-486 as a starting template, we conducted a series of molecular modeling and QSAR studies to determine the structure activity relationship of this drug and other ligands to the hPR protein to discover novel nonsteroidal hPR inhibitors with acceptable ADME profiles. These studies resulted in a class of nonsteroidal RU-486 analogues whose general structure is shown in Figure 1.

The designed compounds are a class of molecules mimicking the B/C rings in the RU-486 tetracyclic backbone. The overlay of a representative compound **1** with RU-486 indicates that this class of compounds closely matches the RU-486 template (Figure 1B). Modeling studies and interesting synthetic challenge centering around the introduction of 1,3-diaxial alkyl, aryl moiety prompted us to synthesize this class of compounds.

A probable synthetic difficulty lies in the assembly of five chiral centers, two of which form a *trans*-fused decalin system bearing a β-9-aryl functionality extending to the same face as the 5-angular proton as well as the 7-methyl group. These substantial challenges arise from the need to stereoselectively assemble a β-9-aryl functionality that occupies an energetically disfavored axial configuration. On the basis of the synthetic difficulties mentioned above, a reasonable retrosynthetic analysis is presented in Figure 2.

An aspect of the current synthetic plan involved an axial sulfide tether set to deliver the phenyl ring to the 9-position from the β-face, ensuring the axial configuration of the 9-aryl functionality. Critical to the success of this approach was the clean epoxidation of **4** to α-epoxide **5a**, which is itself a suitable electrophile for diaxial opening by a nucleophilic aryl sulfide, leading to formation of a C6 axial phenyl sulfide such as **6** (Figure 2). Practically, the epoxidation of the known compound **4**[3] with *m*-CPBA sluggishly afforded a mixture of α- and β-epoxides **5a** and **5b** in 55% yield with the required α-epoxide predominating (α:β = 8:2; based on ^{1}H NMR). Changing the

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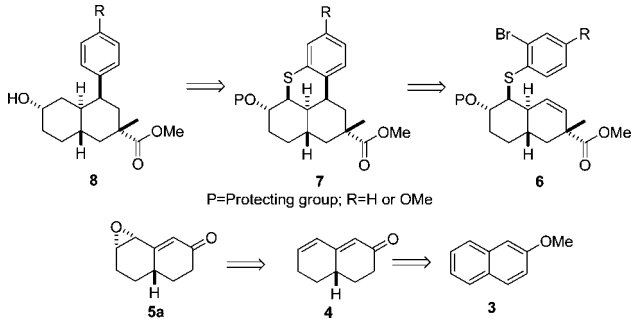
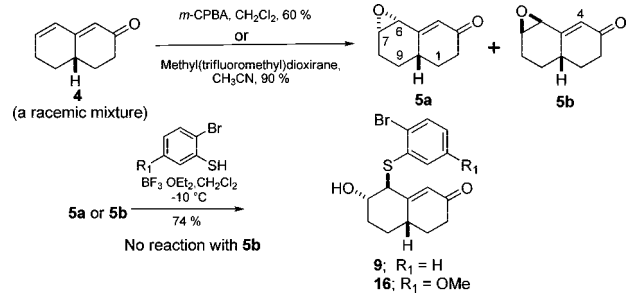


FIGURE 2. Retrosynthetic analysis of the basic framework of the RU-486 analogues.

SCHEME 1. Epoxidation and Epoxide-Opening Reactions



oxidant to 3-methyl-3-trifluoromethyl-1,2-dioxirane[4] dramatically reduced the reaction time to 2 h, and furnished an isolated yield of 90% (α:β = 7:3). Separation of the two isomers by flash column chromatography proved quite difficult, thus the subsequent epoxide-opening reaction with *o*-bromobenzenethiol[5] was performed on the mixture. Interestingly, the reaction proved to be stereospecific and provided only the wanted *trans* diaxial opening alcohol **9** in 92% yield with respect to α-epoxide **5a** (Scheme 1).

The observed stereoselectivity in the epoxide opening reaction was consistent with the well-established Fürst−Plattner rule.[6] Associated with the rigid "*bis*-chair-like" conformation of the decalone ring system, the stereoselectivity of the epoxide opening reaction in the current case was determined by stereoelectronic effects. Results of ab initio calculations[7] were gratifyingly consistent with the experimentally based Fürst−Plattner rule. Accordingly, ArSH-promoted α-epoxide opening is expected to occur more readily in this case than the β-epoxide by a ratio greater than 95:5. This calculated "substrate selectivity" is in close agreement with the experimentally derived ratio of 8:2, thus providing additional support for the Fürst−Plattner rule.

Protection of **9** with MOMCl gave the MOM acetal **10**. To install an axial methyl group and an equatorial ester group both at the 2-position, the Mander carbomethoxylation reaction[8] of **10** followed by methylation of the β-ketoester enolate of **10** was investigated for its stereochemical outcome. We anticipated

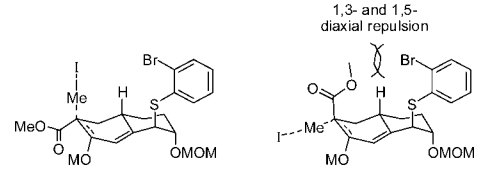


FIGURE 3. Stereoelectronic controlled elaboration of the C-7 quaternary center.

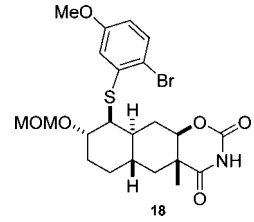
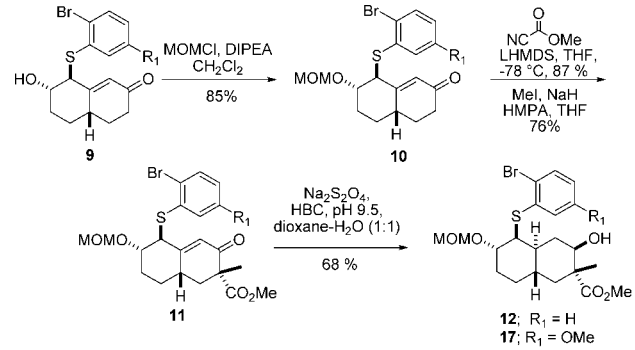


FIGURE 4. The relative stereochemistry of the oxazine-2,4-dione **18**.

SCHEME 2. The Synthesis of the Thioether 12



that in the methylation step, the stronger 1,3- and 1,5-repulsive interaction between the bulky ester group and the axial-thioaryl ring could prevent the ester group from being assembled in the energetically disfavored axial position (Figure 3).[9] Treatment of **10** with LHMDS followed by addition of a molar equivalent of methyl cyanoformate afforded the β-ketoester. Slow addition of the starting material to base proved essential to ensure the success of the reaction. Treatment of the β-ketoester intermediate with MeI in the presence of NaH at 0 °C furnished methylated β-ketoester **11** in 76% yield (Scheme 2).

Reduction of **11** to the *trans*-fused bicyclic intermediate **12** proved difficult as the demand for stereo- and chemoselectivity excluded many commonly used reductive methods. Among the tested reduction methods, including catalytic hydrogenation,[10] PII-catalyst,[11] and copper(I) hydride cluster ([$(Ph_3P)CuH]_6$),[12,13] sodium dithionite reduction[14–16] provided the best result.

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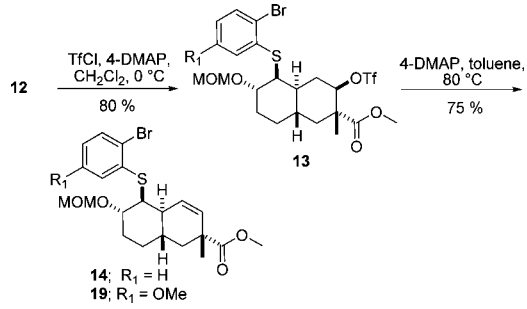
SCHEME 3. Synthesis of β,γ-Unsaturated Ester 14

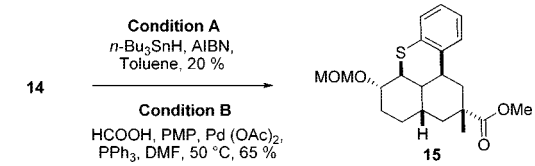


The relative configuration of **12** was determined by 1D- and 2D-NMR spectroscopy and single-crystal X-ray crystallography on its analogue, compound **18** (Figure 4; for its ORTEP drawing, see the Supporting Information).[31] The heterocycle 1,3-oxazin-2,4-dione **18** was prepared by treatment of **17**, the 5′-methoxy derivative of **12**, with 2,2,2-trichloroacetyl isocyanate followed by in situ ring formation after hydrolysis of the 2,2,2-trichloroacetylamide with sodium bicarbonate.

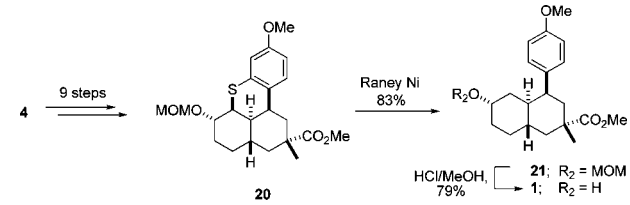
Elimination of the 3-hydroxyl group in **12** to the olefin intermediate **14** provided a key precursor for the subsequent ring closure. This transformation was somewhat more problematic than expected, however. The congested hydroxyl group made activation with a bulky reagent, such as tosyl chloride, problematic. Direct dehydration with methods including Al_2O_3,[17] $POCl_3$,[18] DBU,[19] copper(II) triflate,[20] and even Burgess' reagent[21,22] proved in vain. Converting the alcohol to mesylate and dehydration by $LiCO_3$/LiBr in DMF[23] also failed in our hands. Xanthate pyrolysis[24,25] was also tested. Although the xanthate had been successfully synthesized, the subsequent thermolysis did not work under 200 °C, and higher temperatures resulted in decomposition products. Finally, by conversion of the hydroxyl group to a triflate **13**[26,27] elimination occurred to give the required olefin **14** in 75% yield (Scheme 3).

Subsequently, compound **14** was subjected to an intramolecular cyclization to construct a tricyclic ring system. The intramolecular free radical condensation occurred at 140 °C in toluene in a sealed tube and gave the wanted cyclized product **15** in 20% yield (Conditions A). Further investigation suggested that the low yield could be due to competitive desulfurization, causing cleavage of the phenylsulfide tether before the cyclization. Optimized reaction conditions did not improve the reaction yield dramatically. Furthermore, the high dilution conditions required were unfavorable for scale-up. Next, we examined an intramolecular reductive Heck reaction.[28,29] Though the desulfurization side reaction remained a problem, under the new conditions (Conditions B), the required product **15** was formed in 50% isolated yield (Scheme 4). Switching from TEA to the sterically hindered base pentamethylpiperidine (PMP)-curtailed desulfurization side reaction[30] led to improvement of yield to 65%.

SCHEME 4. Intramolecular Cyclization of Unsaturated Ester 14



SCHEME 5. Synthesis of the Target Compound 1



To this end, the basic framework of the target molecule was successfully synthesized, which proved that the current synthetic pathway is feasible. In accordance with the original design, we applied the present route to synthesize **20** with an electron-rich methoxyl group at the 4′-position. Compound **20** has been successfully synthesized following the established synthetic route, with some minor modifications to achieve the best results, e.g., the epoxide-opening reaction was changed to run in a DMF/acetonitrile system mediated by Cs_2CO_3 to avoid the dehydration as a side reaction. The final steps involved cleavage of the sulfide tether to release the phenyl ring and deprotection of the MOM protecting group to expose the 7-hydroxyl group for further diversification as shown in Scheme 5.

In summary, the framework of the designed target molecules has been synthesized through an efficient 13-step stereoselective pathway from commercially available compound **3** in an overall yield of 6%. By applying this established synthetic route, several diversified analogues of the target molecule have been synthesized. The preliminary bioassay results of **1** and its oxalate derivative were found to be very weakly active (<20%) candidates for hPR ligands. However, the established synthetic route paves a path to expand the spectra of this simple and this novel class of nonsteroidal hPR ligands. An asymmetric variant of the current synthesis and the diversified analogues of the target hPR antagonists for chemical biology studies will be reported in due course.

Experimental Section

Compound 14. To a solution of ester **12** (200 mg, 0.42 mmol) in DCM (2 mL) was added DMAP (150 mg, 1.23 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then trifluoromethanesulfonyl chloride (80 mg, 0.5 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h, poured to ice water, and extracted by DCM (3 × 5 mL). The organic layers were combined, washed with brine, and dried over Na_2SO_4. After removal of solvent under reduced pressure, the resulting residue was purified

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(31) The supplementary crystallographic data can be obtained free of charge from The Cambridge Crystallographic Data Centre, ref. no. CCDC 678950, via www.ccdc.cam.ac.uk/data_request/cif.

by silica gel chromatography (20% hexanes in ethyl acetate) to provide the required triflate **13** as a colorless oil (200 mg, 80%), which was directly used for the next dehydration step.

To a solution of triflate **13** (200 mg, 0.33 mmol) in toluene (2 mL) was added DMAP (100 mg, 0.8 mmol). The reaction mixture was stirred at 80−90 °C for 2 h, and then poured into ice water. The reaction mixture was extracted by diethyl ether (3 × 5 mL). The organic layers were combined, washed with brine, and dried over Na_2SO_4. The organic layer was filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (30% hexanes in ethyl acetate) to provide the wanted compound **14** as a colorless oil (110 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 8.0 Hz, 1 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.28 (dd, J = 8.0, 8.0 Hz, 1 H), 7.08 (dd, J = 8.0, 8.0 Hz, 1 H), 5.82 (d, J = 10.0 Hz, 1 H), 5.60 (d, J = 10.0 Hz, 1 H), 4.65 (ddd, J = 7.0, 7.0, 7.0 Hz, 2 H), 3.89 (d, J = 2.5 Hz, 1 H), 3.74 (s, 3 H), 3.63 (br s, 1 H), 3.37 (s, 3 H), 2.75 (br s, 1 H), 2.20 (br dd, J = 12.5, 12.5 Hz, 1 H), 1.81 (m, 2 H), 1.75 (m, 1 H), 1.49 (m, 2 H), 1.39 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 136.8, 133.2, 131.2, 131.0, 129.5, 127.7, 127.5, 125.9, 95.8, 75.3, 55.6, 52.3, 51.9, 44.8, 39.9, 39.4, 31.1, 27.7, 26.4, 26.1; IR ($CHCl_3$) 2925, 1731, 1578, 1463, 1237, 1101, 1034 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{21}H_{27}O_4SBrK$ 493.0451, found 493.0461.

Compound 15. To a solution of $Pd(OAc)_2$ (10 mg, 0.045 mmol), Ph_3P (26 mg, 0.1 mmol), pentamethylpiperidine (125 mg, 0.145 mL, 0.8 mmol), and formic acid (20 mg, 0.43 mmol) in anhydrous DMF (2 mL) was added ester **14** (100 mg, 0.22 mmol). The reaction mixture was heated to 50 °C for 6 h, and then allowed to cool to room temperature. The reaction mixture was poured into ice water and extracted with ethyl acetate (3 × 5 mL). The organic layers were combined, washed with brine, and dried over sodium sulfate. The organic layer was filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (30% hexanes in ethyl acetate) to provide the required compound as a colorless oil (54 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 2 H), 7.01 (m, 2 H), 4.62 (m, 2 H), 3.98 (s, 1 H), 3.83 (s, 1 H), 3.72 (s, 3 H), 3.35 (s, 3 H), 3.23 (br s, 1 H), 2.71 (d, J = 13.5, 6.0 Hz, 1 H), 2.16−1.40 (m, 9 H), 1.21 (s, 3 H); HRMS (TOF ES$^+$) calcd for $C_{19}H_{23}O_2S$ [M$^+$ − MOM] 315.1419, found 315.1434.

Compound 21. To a suspension of Raney 2800 Nickel (1 mL) in ethanol (5 mL) was added a solution of **20** (50 mg, 0.13 mmol) in ethanol (1 mL). The reaction mixture was heated to reflux for 1 h and then allowed to cool to room temperature. The reaction mixture was filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (30% hexanes in ethyl acetate) to provide the required compound as a colorless oil (40 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, J = 8.0 Hz, 2 H), 6.83 (d, J = 8.0 Hz, 2 H), 4.62 (ddd, J = 8.0, 8.0, 8.0 Hz, 2 H), 3.88 (s, 1 H), 3.81 (s, 3 H), 3.69 (s, 3 H), 3.35 (s, 3 H), 3.10 (ddd, J = 7.0, 7.0, 7.0 Hz, 1 H), 2.25 (dd, J = 13.5, 6.0 Hz, 1 H), 1.90 (m, 3 H), 1.79 (m, 1 H), 1.65 (m, 3 H), 1.46 (m, 2 H), 1.30 (m, 2 H), 1.14 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 157.2, 136.2, 129.9 × 2, 113.2 × 2, 94.7, 72.2, 55.4 × 2, 52.1, 42.6, 41.0, 40.9, 40.3, 36.9, 34.9, 33.9, 30.6, 29.2, 25.8; IR ($CHCl_3$) 2918, 1730, 1039 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{22}H_{32}O_5Na$ 399.2147, found 399.2135.

Compound 1. To a solution of ester **21** (40 mg, 0.10 mmol) in MeOH (2 mL) was added a trace amount of HCl. The reaction mixture was heated to reflux for 1 h and then allowed to cool to room temperature. The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (60% hexanes in ethyl acetate) to provide the required compound as a colorless oil (30 mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J = 8.5 Hz, 2 H), 6.83 (d, J = 8.5 Hz, 2 H), 4.10 (s, 1 H), 3.81 (s, 3 H), 3.69 (s, 3 H), 3.10 (ddd, J = 7.5, 7.5, 7.5 Hz, 1 H), 2.24 (dd, J = 13.5, 6.0 Hz, 1 H), 1.94 (m, 1 H), 1.82 (m, 2 H), 1.74 (m, 1 H), 1.65 (m, 1 H), 1.54 (m, 3 H), 1.31 (m, 2 H), 1.14 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 157.2, 136.2, 129.9 × 2, 113.2 × 2, 67.1, 55.4, 52.1, 42.6, 40.9, 40.8, 40.2, 37.0, 36.3, 34.1, 32.9, 28.6, 26.0; IR ($CHCl_3$) 3416, 2923, 1729, 1511, 1247 cm^{-1}; HRMS (TOF ES$^+$) calcd for $C_{20}H_{27}O_3$ 315.1960, found 315.1955.

Acknowledgment. The authors wish to thank Dr. Jiangnan Peng in the Department of Pharmacognosy at the University of Mississippi for his technical assistance.

Supporting Information Available: Characterization data, crystallographic data for **18**, and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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