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Synthesis of metapristone through an efficient *N*-demethylation of mifepristone†

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Accumulating evidence demonstrates that mifepristone (RU486) exhibits potent anti-proliferative effects on various cancer cell lines. Our recent work shows that its major metabolite metapristone (RU42633) is a good drug candidate for cancer metastatic chemoprevention. However, lack of an efficient method for synthesizing metapristone limited its further clinical development. Herein, an improved and efficient condition of *N*-demethylation of mifepristone with an excellent yield is described. The procedure presented here has several advantages including one-pot preparation, ease of synthesis, and large-scale feasibility.

As one of the essential medicines on the WHO model list, mifepristone (RU486, Fig. 1) with potent antiglucocorticoid and antiprogestogen was widely used clinically for medical termination of pregnancy.[1,2] Pharmacokinetic studies have shown that *N*-monodemethyl mifepristone (RU42633, metapristone) is the most predominant metabolite after oral administration of mifepristone.[3–5] Blood concentrations of metapristone are equal to or even higher than those of mifepristone.[6,7] In addition, metapristone showed the AUC (area under the curve) level higher than mifepristone.[8,9] Recent extensive studies indicated that mifepristone exhibited potent anti-proliferative effects on various cancer cell lines.[10–12] Notably, the solubility and stability of metapristone are both higher than mifepristone.[13] Considering its relative safety and distinctive pharmacological effects, our recent work indicated that metapristone was suitable for cancer metastatic chemoprevention.[14] Therefore, an easy and efficient method for synthesis of metapristone is essential for preclinical studies and further chemical optimization. Despite the availability of three conditions for *N*-demethylation of mifepristone, they are not applicable for large-scale preparation (Fig. 1). For example, Schramm *et al.* reported that a one-step procedure for *N*-demethylation of mifepristone to prepare metapristone by using CaO (base) and iodine in methanol resulted in a yield of 28%.[15] The extremely low yield limited its further application.[16,17] Geldern *et al.* developed a two-step procedure for the *N*-demethylation of mifepristone by using TPAP/NMO (tetra-*n*-propylammonium perruthenate/*N*-methyl morpholine-*N*-oxide) to provide the desired product for the total yield of about 50%.[18] However, TPAP is a very expensive and rare metal reagent.[19] In addition, harsh conditions and the complex purification process made this method inaccessible to obtain sufficient quantities of the desired compound for further preclinical studies. Goldrick *et al.* also reported that the desired product could be obtained by reacting mifepristone with $PhI(OAc)_2$ in a 10% yield.[20]

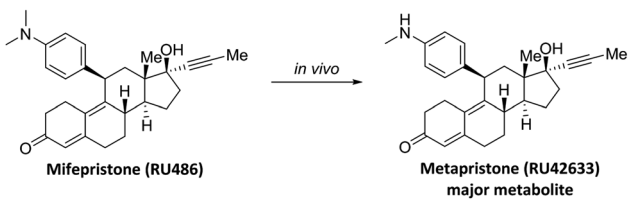

Fig. 1 Major metabolic pathway of mifepristone *in vivo* and general reagents and conditions for synthesis of metapristone from mifepristone. Method A: CaO, I_2, MeOH/THF, 0 °C, 28%; method B: (i) TPAP, NMO, CH_2Cl_2, 63%; (ii) aq. HCl, MeOH, 86%; method C: $PhI(OAc)_2$, CH_3CN/CH_2Cl_2, room temperature, overnight, 10%.

To overcome this obstacle, our group aimed at developing a suitable *N*-demethylation condition for large-scale preparation of metapristone. We first examined several available and mild conditions for *N*-demethylation including NIS/CH_3CN and $TiCl_4/CH_2Cl_2$.[21,22] However, these methods resulted in a complex mixture. We then turned our attention to the previous reported relative cost-effective condition (CaO/I_2). As shown in Table 1, mifepristone treating with 10 eq. of CaO and 3 eq. of I_2 in MeOH/THF at 0 °C for 8 h afforded the desired product in 29%

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† Electronic supplementary information (ESI) available: Copies of ^1H, ^{13}C NMR and HRMS spectra of metapristone, and photographic guide for synthesis of metapristone. See DOI: 10.1039/c5ra26557f

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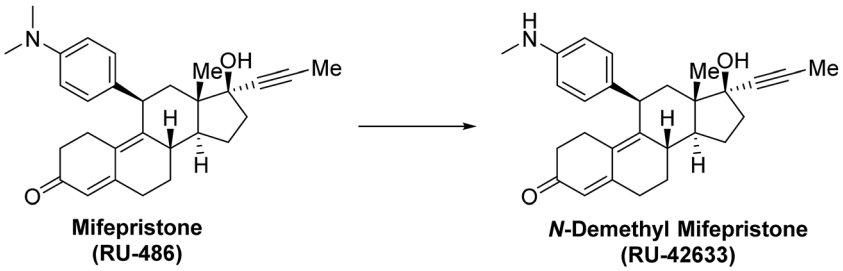
Table 1 Optimization of reaction conditions of metapristone[a]



Entry	Base	I_2[b]	Temperature (°C)	Time (h)	Yield[c] (%)
1	CaO (10 eq.)	3 eq.	0	8	29
2	DBU (10 eq.)	3 eq.	25	24	3
3	$CaCl_2$ (10 eq.)	3 eq.	25	5	3
4	LiF (10 eq.)	3 eq.	25	24	10
5	K_2HPO_4 (10 eq.)	3 eq.	25	24	18
6	KH_2PO_4 (10 eq.)	3 eq.	25	24	10
7	$KHCO_3$ (10 eq.)	3 eq.	25	24	25
8	Cs_2CO_3 (10 eq.)	3 eq.	25	24	20
9	Na_2CO_3 (10 eq.)	3 eq.	25	24	37
10	Li_2CO_3 (10 eq.)	3 eq.	25	24	61
11	K_2CO_3 (10 eq.)	3 eq.	25	24	60
12	NaOAc (10 eq.)	3 eq.	25	24	79
13	KOAc (10 eq.)	3 eq.	25	24	82
14	$NaOCOCF_3$ (10 eq.)	3 eq.	25	24	2
15	LiOAc (10 eq.)	3 eq.	25	24	93
16	LiOAc (5 eq.)	3 eq.	25	24	97
17	LiOAc (3 eq.)	3 eq.	25	24	90
18	LiOAc (5 eq.)	2 eq.	25	24	75
19	LiOAc (5 eq.)	1 eq.	25	24	45
20	LiOAc (5 eq.)	0.5 eq.	25	24	30
21[d]	LiOAc (5 eq.)	3 eq.	25	24	92

[a] Concentration was 0.044 M in THF/MeOH. [b] Concentration was 100 mg mL^{-1} in MeOH. [c] Isolated yield. [d] Gram scale.

yield (entry 1). Note that about 70% of the starting material was recovered. We also noticed that most of CaO was insoluble in MeOH/THF, indicating that a large amount of CaO did not participate in the reaction.

Based on the above precedents, we hypothesized that judicious choice of a suitable base might play an important role in *N*-demethylation. Therefore, various bases were evaluated at room temperature in order to improve efficiency and potential large-scale application (Table 1, entries 2–15). Our efforts were quickly rewarded, as metapristone was obtained at a higher yield when we used Na_2CO_3 or K_2CO_3 or Li_2CO_3 as a base (Table 1, entries 9–11). The use of DBU, $CaCl_2$, LiF, K_2HPO_4, KH_2PO_4, $KHCO_3$ or Cs_2CO_3 as a base only provided the desired product at a low yield (Table 1, entries 2–8). Notably, metapristone was isolated in a significantly higher yield (79%) when using NaOAc as a base (Table 1, entry 12). Other similar bases (KOAc, $NaOCOCF_3$ and LiOAc) were further examined (Table 1, entries 13–15). To our delight, LiOAc was found as the best base to provide metapristone at a 93% yield (Table 1, entry 15). We also noticed that only a small part of LiOAc was visible as a white solid in the reaction mixture. Therefore, diverse amounts of LiOAc were further evaluated (Table 1, entries 16–17). Upon reducing the amount of LiOAc (5 eq., 3 eq.), the yields of the desired product were 97% and 90%, respectively. Also, no visible LiOAc was observed in the reaction mixture. Thus, 5 eq. of LiOAc was the best amount for this reaction. It is worth mentioning that the solubility of LiOAc in MeOH is the highest in all three metal acetates (LiOAc: 30.37 g/100 g MeOH, KOAc: 24.24 g/100 g MeOH, NaOAc: 16.00 g/100 g MeOH at 15 °C),[23] further indicating that the solubility of an inorganic base in organic solvents is quite important for *N*-demethylation. Different amounts of I_2 were also evaluated (Table 1, entries 18–20). However, reducing the amount of I_2 (2 eq., 1 eq., 0.5 eq.), the yield of metapristone was decreased. Hence, the condition of entry 16 (5 eq. of LiOAc and 3 eq. of I_2) should be used as the best reaction condition. Gratifyingly, this improved condition was employed on the gram scale to afford metapristone at a 92% yield (entry 21; see also Fig. S1–S5†).

In summary, the concise and efficient synthetic approach to access metapristone was achieved for the first time at a high yield by using the improved condition. We determined that LiOAc is a superior base for *N*-demethylation of mifepristone.

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The established condition facilitated ongoing preclinical evaluation of metapristone for cancer metastatic chemoprevention. The synthesis of new mifepristone analogues as novel anticancer agents as well as potential cancer metastatic chemopreventive agents is currently underway.

Experimental section

General procedure (Table 1, entry 16) for *N*-demethylation of mifepristone (8*S*,11*R*,13*S*,14*S*,17*S*)-17-hydroxy-13-methyl-11-(4-(methylamino)phenyl)-17-(prop-1-yn-1-yl)-1,2,6,7,8,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one

To a solution of mifepristone (86 mg, 0.2 mmol) in 3 mL THF was added I_2 (152 mg/1.52 mL MeOH, 0.6 mmol) and LiOAc (132 mg, 1.0 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 24 h. Then, the mixture was diluted with EtOAc (15 mL), washed with H_2O (10 mL) followed by 5% aqueous $Na_2S_2O_3$. The organic layer was washed with H_2O (10 mL) followed by saturated brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude reaction mixture. The residue was purified by silica gel chromatography (petroleum ether/EtOAc = 1/1) to give the desired product metapristone (81 mg, 97%). HPLC purity >98% (t_R = 5.67 min).[14] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, J = 7.8 Hz, 2H), 6.53 (d, J = 7.4 Hz, 2H), 5.75 (s, 1H), 4.33 (d, J = 6.3 Hz, 1H), 3.62 (s, 1H), 2.80 (s, 3H), 2.78–2.69 (m, 1H), 2.64–2.54 (m, 2H), 2.51–2.40 (m, 2H), 2.38–2.28 (m, 3H), 2.27–2.17 (m, 2H), 2.04–1.93 (m, 2H), 1.88 (s, 3H), 1.77–1.67 (m, 2H), 1.54–1.41 (m, 1H), 1.39–1.27 (m, 1H), 0.55 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.76, 157.08, 147.26, 146.92, 133.01, 129.20, 127.75, 122.81, 112.70, 82.55, 82.51, 80.29, 49.94, 46.98, 39.80, 39.28, 39.05, 38.99, 37.00, 31.25, 30.95, 27.49, 25.93, 23.44, 13.80, 3.94. HRMS (ESI) calcd for $C_{28}H_{34}NO_2$ $(M + H)^+$ m/z 416.2584, found 416.2589.

Conflicts of interest

The authors declare no competing financial interest.

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