ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

Communication

Optimized Synthetic Route for Enantioselective Preparation of (S)-Metolachlor from Commercially Available (R)-Propylene Oxide

Peng Yang, Xiao Wang, Lin Peng, Feng Chen, Fang Tian, Chao-Zhe Tang, and Li-Xin Wang

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.7b00216 • Publication Date (Web): 06 Sep 2017

ACS Publications

Organic Process Research & Development is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

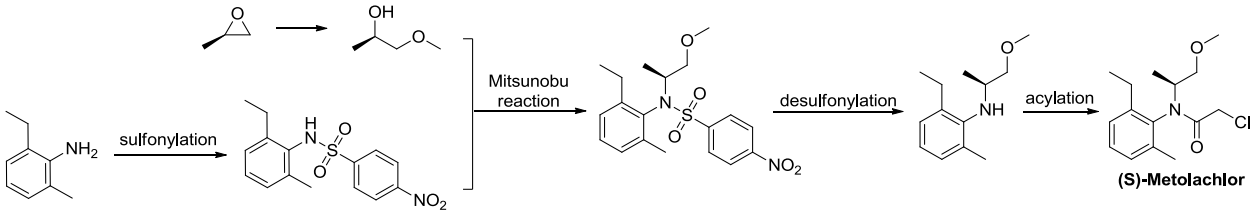
Optimized Synthetic Route for Enantioselective Preparation of (S)-Metolachlor from Commercially Available (*R*)-Propylene Oxide

Peng Yang,[†,‡] Xiao Wang,[†,‡] Lin Peng,[†] Feng Chen,[†,‡] Fang Tian,[†,‡] Chao-Zhe Tang,[†] and Li-Xin Wang[,†]*

[†]Key Laboratory of Asymmetric Synthesis and Chirotechnology of Sichuan Province, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, P.R. China

[‡]University of Chinese Academy of Sciences, Beijing 100049, P.R. China

TOC graphic


sulfonylation
Mitsunobu reaction
desulfonylation
acylation
(S)-Metolachlor

Abstract

An enantioselective preparation of (*S*)-Metolachlor has been accomplished. The synthetic route featured the asymmetric preparation of chiral intermediates, and the final (*S*)-Metolachlor from commercially available (*R*)-propylene oxide and a key Fukuyama's process. The key steps, control points, separation-purifications and the whole process are optimized, and the target compound has been successfully prepared in five steps in 51-55% overall yield with excellent enantioselectivity (99% ee) up to a 30 gram scale. By judicious choice of synthetic route and selection of starting materials and intermediates, no column chromatographic methods are needed for separation and purification of the intermediates and the final products. The same strategy was extended as a general method for a series of pesticides and herbicide analogs of Metalaxyl-M and Dimethenamid-P.

Keyword: (S)-Metolachlor, Fukuyama's process, (R)-propylene oxide, enantioselective preparation

Introduction

Chiral herbicide (*S*)-Metolachlor (Figure 1) is the active ingredient of Dual Magnum, one of the most important grass herbicides using in maize and a wide range of other crops. Due to its great importance in agrochemicals, the synthesis of (*S*)-Metolachlor has become an area of intense interests in synthetic chemistry.[1–3] The key point for its preparation lies in the effective construction of amino chiral center. In the past 20 years, most synthetic approaches have focused on the asymmetric hydrogenations of sterically hindered imines,[1d, 1g, 2] and the most outstanding example is the Ir-xyliphos catalyzed chiral reduction of MEA imine in 1996 and Hans-Ulrich Blaser has well reviewed the evolution of the current industrial hydrogenation process.[2b] Other strategies, such as microbial transformation, chiral agent reduction[4] and chiral pool preparations,[5] have become a new and powerful reservoir for the potential preparations of (*S*)-Metolachlor. As a part of our continued interests in process chemistry,[6–8] herein we wish to report an optimized route for the enantioselective preparation of (*S*)-Metolachlor and its analogs from commercially available (*R*)-propylene oxide and L-lactic acid methyl ester.

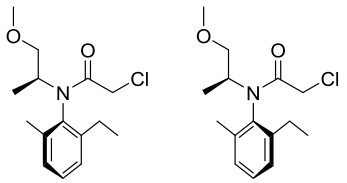


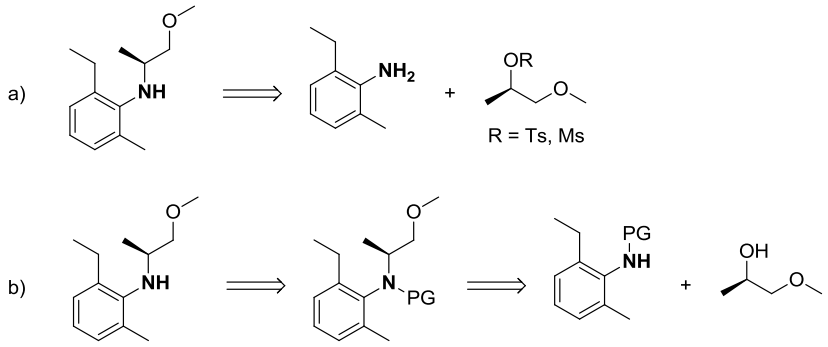
Figure 1. The structure of (*S*)-Metolachlor

Results and Discussion

In a preliminary study, we tried the potential "optimal" direct nucleophilic substitution of (R)-methoxyisopropanol Ts/Ms derivatives with 2-methyl-6-ethyl-benzamine.[2b] The reaction was conducted with 2.0 equiv. 2-methyl-6-ethyl-benzamine, 1.0 equiv. Ts/Ms derivatives and 1.2 equiv. pyridine in DMF at room temperature to 160 ^{o}C. As a whole, the expected substitution is disappointedly inactive (generally < 10% conversion) or racemized (58-90% ee) at higher temperature (with slightly higher conversion) (Scheme 1a). The similar attempt and problems were also mentioned by Hans-Ulrich Blaser.[2b] Those results prompted us to carefully reconsider

this synthetic route centering on modifications to both electrophilic and nucleophilic partners in the substitution step (Scheme 1b).

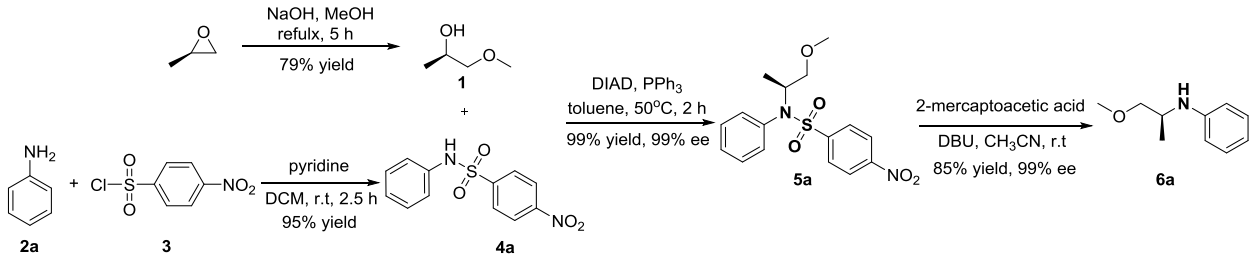
Scheme 1. Strategy for the Preparation of (*S*)-Metolachlor



Scheme 2 summarized our synthetic strategy, as well as the key intermediates and starting materials we identified. To further optimize each reaction step, cheap and easily available aniline **2a**, which contained the similar nucleophilicity with 2-ethyl-6-methylaniline, was used as the model substrate. Based on a well-established hydrolytic ring-opening reaction, we selected (R)-propylene oxide (99% ee) as the commercial precursor for (R)-1-methoxypropan-2-ol **1**, the starting material required for a Fukuyama-type Mitsunobu alkylation,[9] which is known to proceed with complete inversion of chirality. For synthetic route, we always cherish our persistence of "separation-purification and process oriented industrial organic syntheses", and in every synthetic step, all the reactants, intermediates and the formed substances should be with obvious differences in physical and chemical characteristics, such as solubility, boiling point, polarity, acidity and basicity, for easier separation-purifications before synthetic route, reaction, solvent and technique selections. Based on those considerations, our synthetic route featured the following characteristics: the starting aromatic amine and pyridine (basic, easy salt formation and soluble in water), quite different from the sulfonamide **4** and can be easily separated and purified by simple and general acidification/extraction work-up. After Fukuyama's process, sulfonamide **4** and **5**, with different solubility in sorts of solvents, and may be separated and purified by recrystallization of **4** or just washing with solvent. Sulfonamide **5** (neutral) and the key intermediate **6** (basic, easy salt formation and soluble in water) with obvious differences in physical and chemical characteristics, can also be easily separated and purified by simple and general acid/base work-up. Basic amines **6** are also readily separated from the neutral

sulfonamides **4** and **5** by aqueous extraction at low pH. We expect the described formal synthesis of the herbicide targets to be readily scalable.

Scheme 2. Preparation and optimizations of the model reaction

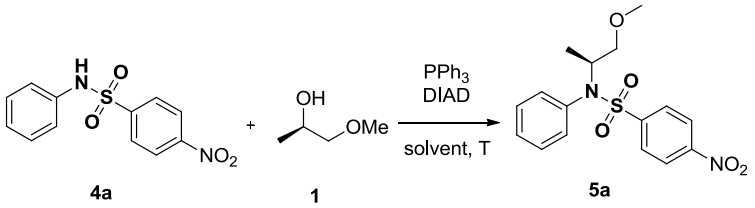


For the manufacture of **1** from (*R*)-2-propylene oxide, there existed some known processes for nucleophilic substitution in the presence of a base.[10] The simplest method was Slayton A. Evans' procedure.[10d] (*R*)-2-propylene oxide was ring opened in catalytic sodium hydroxide in refluxing methanol. The residue was neutralized, after vacuum distillation, a distillate composed of 88.7% product and 11.3% of the unwanted 2-methoxy-1-propanol isomer was obtained. To simplify the work-up process and conveniently to reuse methanol, after termination of the reaction, the residue was directly rectified with packed column (column length: 15 cm, specification for spring-like glass packing: diameter 3–8 mm, length 6–20 mm) under atmospheric pressure, the desired (*R*)-1-methoxy-2-propanol was obtained at 113 ^{o}C in 79% yield with 99% purity (GC), and methanol may be recycled without further treatment.

For the whole synthetic route and especially the key Fukuyama's process for the construction of the chiral center, the selections of protected sulfonylation group and effective desulfonylation were two key control steps for successful and effective preparation for the target (*S*)-Metolachlor. In classic Fukuyama's process,[9] an improved variant of Mitsunobu reaction for an easier desulfonylation, 4-nitrobenzenesulfonyl, 2-nitrobenzenesulfonyl or 2,4-dinitrobenzenesulfonyl chloride was generally used. Considering the availability and cost of sulfonyl chlorides, 4-nitrobenzenesulfonyl chloride **3** instead of 4-methylbenzenesulfonyl chloride or other chlorides was used for the sulfonylation of **2a**, and 4-nitro-N-phenylbenzenesulfonamide **4a** was readily prepared in the presence of 1.0 equiv. pyridine and 0.9 equiv. **3** in DCM in 96–98% yields.[11] As a typical preparation method, this process had been reported by several literatures and generally gave good results.[11] However, the purifications were usually limited to column chromatographic

methods, or used only with crude product without purification. We found the crude product of **4a** could be recrystallized with ethanol in 80% yield or just washing with cold ethanol in 95% yield with 98% HPLC purity.

Table 1. Screening for Mitsunobu Reaction of 4a[a]



4a 1 5a

entry	**1 (eq)**	PPh_3 (eq)	DIAD (eq)	T (^oC)	solvent	yield[b] (%)	ee[c] (%)
1	1.0	1.0	1.0	80	toluene	50	99
2	1.2	1.2	1.2	80	toluene	62	99
3	1.2	1.2	1.5	80	toluene	70	99
4	1.2	1.5	1.5	80	toluene	88	99
5	1.5	1.5	1.5	80	toluene	88	99
6	2.0	2.0	2.0	80	toluene	88	99
7	1.2	1.5	1.5	70	toluene	90	99
8	1.2	1.5	1.5	60	toluene	90	99
9	1.2	1.5	1.5	50	toluene	99	99
10	1.2	1.5	1.5	40	toluene	85	99
11	1.2	1.5	1.5	25	toluene	85	99
12	1.2	1.5	1.5	25[d]	toluene	85	99
13	1.2	1.5	1.5	50	THF	trace	nd
14	1.2	1.5	1.5	50	DCE	82	99
15	1.2	1.5	1.5	50	toluene[e]	99	99

[a]Unless otherwise noted, the reaction was performed with **4a** (1.0 mmol), in anhydrous toluene (2.8 mL) for 2 h. [b]Isolated yield. [c]Determined by chiral HPLC. [d] reaction time was increased to 24 h [e]Commercial grade toluene.

After Mitsunobu reaction of **1** and **4a** in the presence of triphenylphosphine and diisopropyl azodicarboxylate (DIAD), the key intermediate **5a** was successfully obtained. Based on Mitsunobu reaction conditions,[12] some important reaction parameters were furtherly investigated (Table 1). The model reaction initially proceeded with 1.0 equiv. **4a**, 1.0 equiv. PPh_3 and 1.0 equiv. DIAD at 80 ^oC in toluene, and product **5a** was obtained in only 50% yield (Table 1, entry 1). To furtherly raise the yield, there were generally two strategies: excessive **1** or excessive **4a** was used and in most and generally regarded opinions, excessive cheaper **4a** was better compared with excessive **1**. In our strategy, the easy separation and purification of any mixture is the most top consideration. Therefore, an excess of water soluble and volatile **1** was used; **4a** and **5** being similar in structure and physical properties. Hence, excessive **1** is more easily separated from **5a** by water washings or distillation. Based on those considerations, various material ratios

were studied (Table 1, entries 2–6), and 88% yield was obtained in 1.2 equiv. **1**, 1.5 equiv. PPh_3 and DIAD (Table 1, entry 4). Higher material ratio gave almost equal results (Table 1, entries 5–6). The temperature also showed some effects on Mitsunobu process, a higher or lower temperature was not suitable (Table 1, entries 7–12), and best result of 99% yield with 99% ee was achieved at 50 ^oC (Table 1, entry 9). Other solvents for Mitsunobu reaction were also studied, and inferior results were obtained (Table 1, entries 13–14). When the commercial grade toluene was used, almost the same excellent result was achieved (Table 1, entry 15, 99% yield, 99% ee).

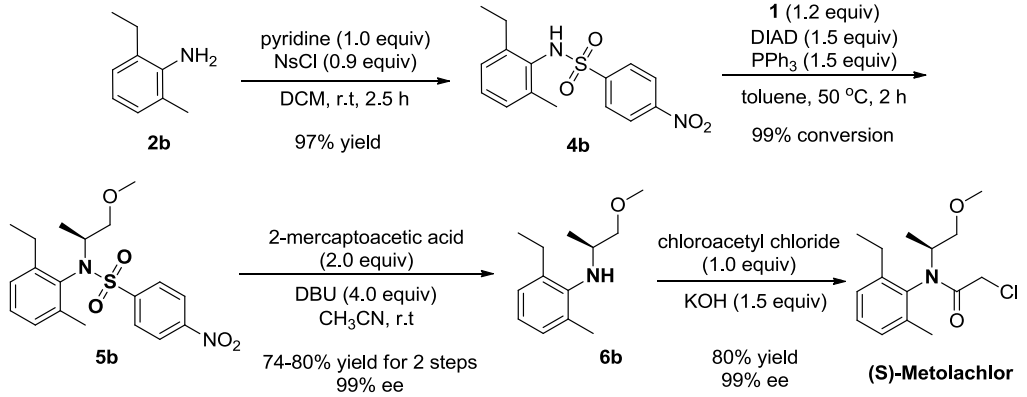
Another key step of Fukuyama's process was the mild and effective desulfonylation. According to Fukuyama's procedures, the intermediate **5a** could be treated with different bases and thiols in acetonitrile (Table 2).[11a, 12, 13] When **5a** was treated with 4.0 equiv. DBU and 2.0 equiv. 2-mercaptoacetic acid (to reduce the loading of DBU, such as a slightly lower to 3.0 equiv., leads to incomplete reaction conversion to 68% yield) at room temperature for 1 h, the desired secondary amine **6a** was obtained in the best result (85% yield, 99% ee, Table 2, entry 3).

Table 2. Desulfonylation of Sulfonamide 5a[a]

entry[a]	base	R-SH	yield[b] (%)	ee[c] (%)
1	K_2CO_3	benzenethiol	72	99
2	LiOH	2-mercaptoacetic acid	82	99
3	DBU	2-mercaptoacetic acid	85	99

[a]Unless otherwise noted, the reaction was performed with **5a** (1.0 mmol), base (4.0 mmol) and thiol (2.0 mmol) in CH_3CN (5 mL) for 2 h. [b]Isolated yield. [c]Determined by chiral HPLC.

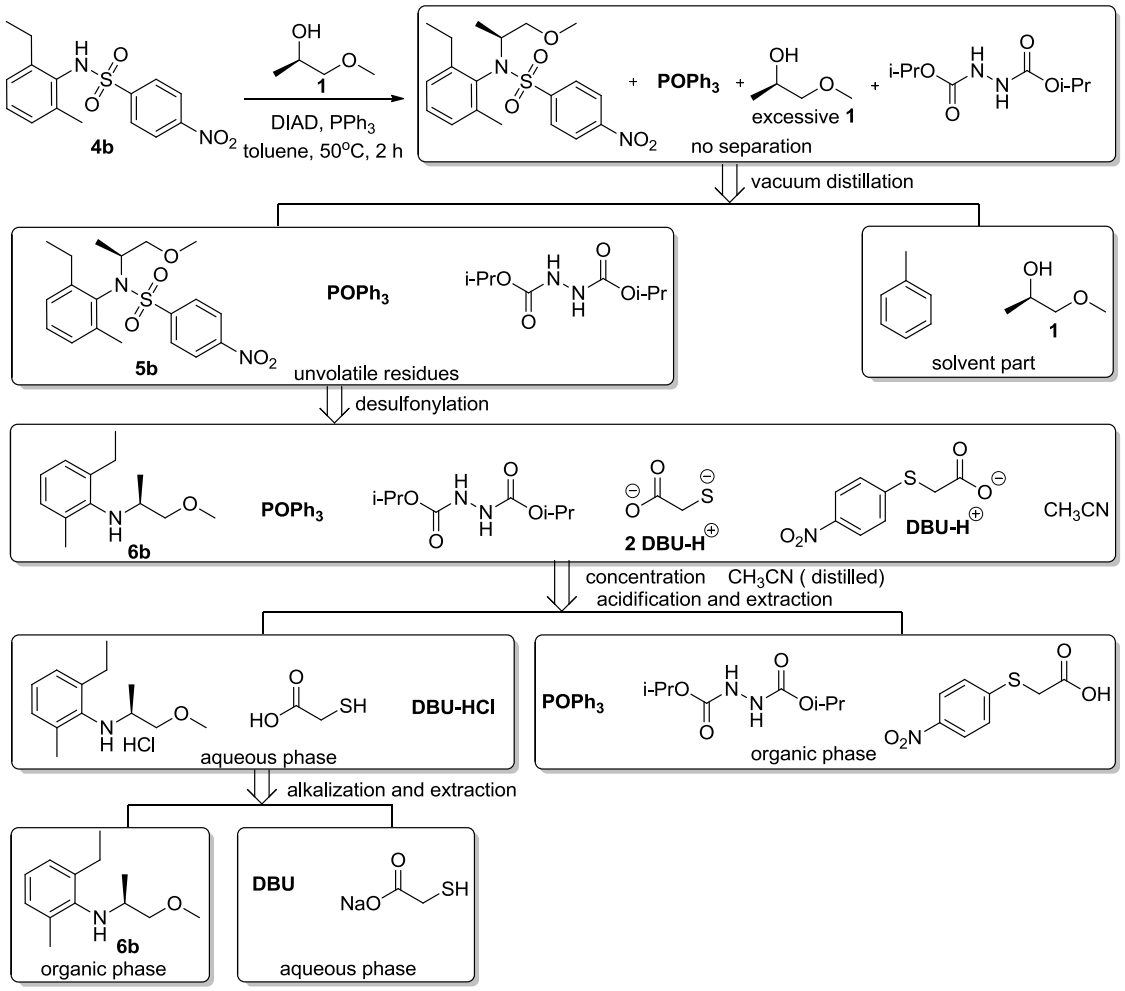
Scheme 3. Enantioselective Preparation of (*S*)-Metolachlor



Under the optimal reaction conditions, we broaden the synthetic route to the preparation of chiral herbicide (*S*)-Metolachlor intermediate **6b** (Scheme 3) and attended to the process and

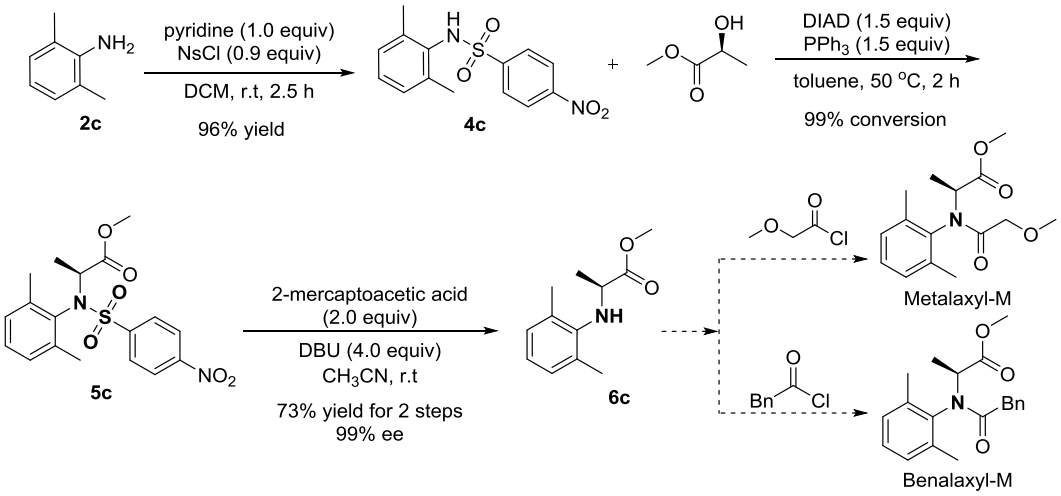
separation-purification optimizations. In the sulfonylation step, the reaction mixture containing **4b** and other excessive reactants, excessive **2b** and pyridine was acidified to pH = 3 or lower for complete salt formation and separated by washing with water, product **4b** stayed in organic phase. After removal of solvent, the crude product was obtained and purified by washing with ethanol to give pure **4b** in 97% yield with 98% HPLC purity. In Mitsunobu step, **4b** displayed the similar reactivity as **4a**. Treatment of **4b** with **1** in toluene smoothly afforded key intermediate **5b** in 99% conversion. After strip of solvent and excessive **1** under reduced pressure, the residue, containing phosphorous byproducts (neutral), quite different with the target **6b** (basic) in physical and chemical properties, was directly used for the subsequent desulfonylation step in one-pot without separation and purification. The desulfonylation was operated in CH_3CN with 2.0 equiv. mercaptoacetic acid and 4.0 equiv. DBU[11a] at room temperature for 1 h, and the residue was treated as the following procedures: The solvent was removed and the residue was acidified to pH = 1 or lower to ensure the desired **6b** to fully form its hydrochloride salt (over 2 h with stirring) and sufficiently soluble in enough water. DCM was added and all neutral byproducts and organic wastes were extracted and separated with **6b** hydrochloride in water. The aqueous phase, containing the needed product, DBU-HCl and mercaptoacetic acid, was basified and extracted with DCM, product **6b** in DCM was separated while water soluble DBU and mercaptoacetic acid stayed in the aqueous phase. The crude product was purified by vacuum distillation and the desired **6b** was obtained in 74%–80% total separated yield[14] for two steps with 99% ee. The principles and strategies for the separation-purification of the needed **6b** with other materials were outlined in Chart 1. Operated as the reported method,[15] **6b** was easily transformed to (*S*)-Metolachlor in 80% yield with 98% HPLC purity in 99% ee.

Chart 1. Material flow and separation-purification strategies for target 6b.



Further applications of this method to the preparations of other chiral bactericides of Metalaxyl-M and Benalaxyl-M were examined (Scheme 4). The whole process and results of this synthetic route were similar to those of (*S*)-Metolachlor, while using commercially available L-lactic acid methyl ester as the chiral pool starting material, **6c** was obtained in 70–74% total yield in three steps. Using different chlorides and after general work-up, the key chiral intermediate of **6c** was easily transformed to Metalaxyl-M[16] and Benalaxyl-M.[17]

Scheme 4. Preparations of Metalaxyl-M and Benalaxyl-M



Conclusions

In conclusion, an optimized enantioselective preparation of (*S*)-Metolachlor from commercially available (*R*)-propylene oxide via Fukuyama's processes has been successfully accomplished. Our synthesis characterized by the careful choice of synthetic route and starting materials and intermediates with simple and general work-up procedures. After optimizations of the key Fukuyama's processes, especially optimizations for every separation-purification, the target compound has been successfully prepared for five steps in 51-55% overall yield with excellent enantioselectivity (99% ee) up to a 30 gram scale without column chromatographic methods. Furthermore, this route can be used as a general method for a series of pesticides and herbicide analogs such as Metalaxyl-M and Benalaxyl-M.

Experimental Section

Materials and Instruments. Unless otherwise noted, all solvents and reagents were purchased from the suppliers and used without further purifications. (R)-2-propylene oxide was commercially available with 99% ee. Mechanic stirrers were used for all stirrings. ^{1}H NMR spectra were recorded on a Bruker DPX 300 MHz spectrometer in $CDCl_3$, DMSO-d_6 with Me_4Si (TMS) as internal standard at room temperature. Mass spectra were recorded on a Bruker micro TOF-Q mass spectrometer. Reaction process and purity were monitored by HPLC analysis on C18 columns. Enantiomeric excess was determined by HPLC analysis on chiralpak AD-H, AS-H, or IC-H columns.

*(R)-1-Methoxypropan-2-ol (**1**).*

In a 500 mL three necked bottle with condenser, (*R*)-2-propylene oxide (75 g, 1.3 mol, 99% ee), sodium hydroxide (1.0 g, 2.5 mmol) and methanol 250 mL were combined and heated to reflux. The mixture was stirred for 5 h, and the condenser was replaced by distillation apparatus. The product was obtained by atmospheric rectification (15 cm packed column, specification for spring-like glass packing: diameter 3–8 mm, length 6–20 mm) at 113 ^{o}C as a colorless liquid (92.2 g, 79% yield, GC 99%). Boiling point in literature:[18] 116-119 ^{o}C (760 mm Hg). Boiling point of 2-methoxy-1-propanol in literature:[18] 127-129 ^{o}C (760 mm Hg). ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.55 (d, J = 4.6 Hz, 1H), 3.75–3.68 (m, 1H), 3.24 (s, 3H), 3.22–3.17 (m, 1H), 3.11 (dd, J = 9.5, 5.3 Hz, 1H), 1.01 (d, J = 5.4 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 78.2, 64.8, 58.3, 20.2.

*4-Nitro-N-phenylbenzenesulfonamide (**4a**).*

To a stirred solution of aniline (46.5 g, 0.5 mol) and pyridine (39.6 g, 0.5 mol) in dichloromethane (460 mL), 4-nitrobenzene-1-sulfonyl chloride (99.8 g, 0.45 mol) was added. After mechanic stirring at ambient temperature for 2.5 h, the reaction mixture was acidified to pH = 3 with 1 N HCl. The resulting organic phase was washed with water (460 mL x 3) and concentrated in vacuum. The residue solid was washed with cold ethanol (80 mL) by stirring and filtered to afford the product as a yellow solid (119 g, 95% yield, HPLC 98%). Mp 177–178 ^{o}C (174–176 ^{o}C[11a]); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.57 (s, 1H), 8.35 (d, J = 8.9 Hz, 1H), 7.97 (d, J = 8.9 Hz, 1H), 7.32–7.19 (m, 2H), 7.14–6.99 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 149.8, 144.9, 136.9, 129.4, 128.3, 124.8, 124.6, 120.7.

*N-(2-ethyl-6-methylphenyl)-4-nitrobenzenesulfonamide (**4b**).*

Preparation of **4b** was similar to that of **4a**. **4b** (279.8 g, 97% yield, HPLC 98%) was obtained from 2-ethyl-6-methylaniline (135.2 g, 1.0 mol) as a yellow solid; Mp 193–195 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.79 (s, 1H), 8.44–8.39 (m, 2H), 7.96–7.92 (m, 2H), 7.17–7.07 (m, 2H), 7.04–7.01 (m, 1H), 2.41 (q, J = 7.4 Hz, 2H), 1.90 (s, 3H), 0.97 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 149.6, 147.4, 143.7, 137.6, 132.0, 128.4, 128.0, 127.9, 126.7, 124.7, 24.1, 18.6, 14.6. HRMS (ESI) m/z calcd for $C_{15}H_{17}N_2O_4S^+$ $(M+H)^+$ 321.0904, found 321.0903.

*N-(2,6-dimethylphenyl)-4-nitrobenzenesulfonamide (**4c**).*

Preparation of **4c** was similar to that of **4a**. Product **4c** (265.8 g, 96% yield, 90% HPLC) was obtained from 2,6-dimethylaniline (121.2 g, 1.0 mol) as a yellow solid; Mp 189–190 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.41 (d, J =8.9 Hz, 2H), 7.94 (dd, J = 9.4, 2.4 Hz, 2H), 7.12–7.02 (m, 3H), 1.96 (s, 6H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 149.6, 147.4, 137.6, 132.8, 128.5, 128.0, 127.6, 124.7, 18.5. HRMS (ESI) m/z calcd for $C_{14}H_{15}N_2O_4S^+$ $(M+H)^+$ 307.0747, found 307.0746.

*(S)-N-(1-methoxypropan-2-yl)-4-nitro-N-phenylbenzenesulfonamide (**5a**).*

For reaction condition screening: To a stirred solution of **4a** (278 mg, 1 mmol), triphenylphosphine (393 mg, 1.5 mmol) and (*R*)-1-methoxypropan-2-ol **1** (108 mg, 1.2 mmol) in toluene (3.2 mL), diisopropyl azodicarboxylate (303 mg, 1.5 mmol) was added at room temperature. The reaction mixture was stirred at 50 ^{o}C for 2 h. The solvent was removed and the residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 20:1–10:1) and 349 mg (99% yield, 99% ee, HPLC 96.5%) of **5a** was obtained as a white solid; Mp 121–122 ^{o}C; $[\alpha]_D^{20}$ = 45.0 (c = 1.75, $CHCl_3$). The ee value was determined by a chiral HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, 99% ee: t_{major} = 25.2 min, t_{minor} = 23.0 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, J = 8.9 Hz, 2H), 7.90 (d, J = 8.9 Hz, 2H), 7.40–7.32 (m, 3H), 7.03 (dd, J = 7.8, 1.2 Hz, 2H), 4.78–4.71 (m, 1H), 3.17–3.10 (m, 4H), 3.00 (t, J = 10.0 Hz, 1H), 1.09 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 146.7, 133.6, 132.4, 129.3, 129.16, 129.15, 123.4, 73.4, 58.1, 55.2, 16.9. HRMS (ESI) m/z calcd for $C_{16}H_{19}N_2O_5S^+$ $(M+H)^+$ 351.1009, found 351.1010.

Scale up preparations: To a mechanic stirred solution of **4a** (55.6 g, 0.2 mol), triphenylphosphine (78.6 g, 0.3 mol) and (*R*)-1-methoxypropan-2-ol **1** (21.6 g, 0.24 mol) in toluene (640 mL), diisopropyl azodicarboxylate (60.7 g, 0.3 mol) was added in ice bath. The addition was completed within 5 min and the reaction mixture was allowed to reach 25 ^{o}C. The reaction mixture was mechanic stirred for additional 2 h at 50 ^{o}C. The solvent was removed and the residue was directly used for the next step without further purification.

*1-Ethyl-2-((2S)-3-methoxy-2-methyl-1-((4-nitrophenyl)sulfonyl)propyl)-3-methylbenzene (**5b**).*

Preparation of **5b** was similar to that of **5a**. Product **5b** (391 mg, 99% yield, HPLC 95.6%) was obtained from **4b** (320 mg, 1.0 mmol) as a semisolid. In the scale up preparation, **5b** was obtained as a crude product and used directly for the next step; $[\alpha]_D^{20}$ = –9.6 (*c* = 1.35, $CHCl_3$); dr = 53/47. The ee value was determined by a chiral HPLC (Chiralcel IC column, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer 98% ee: t_{major} = 33.2 min, t_{minor} = 28.6 min; minor diastereomer 99% ee: t_{major} = 51.2 min, t_{minor} = 25.5 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.6 Hz, 2H), 7.98–7.93 (m, 2H), 7.24–7.20 (m, 2H), 7.11–7.07 (m, 1H), 4.29–4.23 (m, 1H), 3.42–3.38 (m, 1H), 3.35–3.32 (m, 1H), 3.06–3.04 (s, 3 H, Major + Minor), 2.48–2.45 (m, 1H), 2.33–2.31 (m, 1H), 2.10–1.97 (s, 3H, Major + Minor), 1.13–1.01 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 146.72, 146.66, 146.1, 145.3, 140.0, 139.3, 134.2, 134.0, 129.18, 129.15, 128.9, 128.8, 128.61, 128.59, 126.9, 126.8, 124.4, 124.3, 74.5, 74.4, 57.9, 57.79, 57.75, 57.7, 24.7, 23.6, 20.09, 19.0, 15.9, 15.8, 15.0, 14.8. HRMS (ESI) m/z calcd for $C_{18}H_{21}N_2O_6S^+$ $(M+H)^+$ 393.1115, found 393.1116.

*Methyl N-(2,6-dimethylphenyl)-N-((4-nitrophenyl)sulfonyl)-L-alaninate (**5c**).*

Preparation of **5c** was similar to that of **5a**. Product **5c** (382 mg, 97% yield, HPLC 92.4%) was obtained from **4c** (306 mg, 1.0 mmol) and L-lactic acid methyl ester (156 mg, 1.5 mmol) as a white solid. In the scale up preparation, **5c** was obtained as a crude product and used directly for the next step; Mp 129–130 ^oC; $[\alpha]_D^{20}$ = 4.8 (*c* = 1.05, $CHCl_3$). The ee value was determined by a chiral HPLC (Chiralcel OD column, hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm, 98% ee: t_{major} = 15.8 min, t_{minor} = 17.8 min; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.41–8.37 (m, 2H), 7.83–7.78 (m, 2H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.18–7.07 (m, 2H), 4.78 (dd, *J* = 14.3, 7.1 Hz, 1H), 3.72 (s, 3H), 2.08 (s, 3H), 1.93 (s, 3H), 0.94 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.5, 150.0, 144.6, 140.9, 140.3, 133.2, 129.4, 129.1, 129.0, 128.8, 124.3, 57.6, 52.3, 18.9, 18.4, 16.7. HRMS (ESI) m/z calcd for $C_{19}H_{25}N_2O_5S^+$ $(M+H)^+$ 393.1479, found 393.1478.

*(S)-N-(1-methoxypropan-2-yl)aniline (**6a**).*

For reaction condition screening: To a stirred solution of **5a** (349 mg, 1.0 mmol) in acetonitrile (3.5 mL), a solution of DBU (608 mg, 4.0 mmol) and mercaptoacetic acid (184 mg 2.0 mmol) in acetonitrile (1.0 mL) was added. After stirring at ambient temperature for 10–15 min, the solvent was removed and the residue was purified by flash column chromatography on silica gel

(petroleum ether/EtOAc = 20: 1) to afford 140.0 mg (85% yield, 99% ee) of the product **6a** as a colorless oil.

Scale up preparation: To a mechanic stirred solution of crude **5a** (the residue from the previous step) in acetonitrile (700 mL), a solution of DBU (122 g, 0.8 mol) and mercaptoacetic acid (37 g 0.4 mol) in acetonitrile (200 mL) was added. After stirring at ambient temperature for 2 h, the solvent was removed and the residue was acidified by 6M HCl to pH = 1 or lower. The mixture was extracted with dichloromethane (400 mL x 3). The resulting aqueous layer was basified with 5 M NaOH to pH 10 above and extracted with dichloromethane (400 mL x 3). The organic layer was evaporated and purified by vacuum distillation (107 ^{o}C, 5 mm Hg) to afford the product as a colorless oil (23.1 g, 70% yield, GC 99%); $[\alpha]_D^{20}$ = –0.9 (*c* = 0.75, $CHCl_3$). The ee value was determined by a chiral HPLC (Chiralcel OD column, hexane/*i*-PrOH = 99.5/0.5, flow rate 1.0 mL/min, λ = 254 nm, 99% ee: t_{major} = 20.0 min, t_{minor} = 11.9 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07–7.02 (m, 2H), 6.57 (d, *J* = 7.7 Hz, 2H), 6.49 (t, *J* = 7.2 Hz, 1H), 5.27 (d, *J* = 8.0 Hz, 1H), 3.61–3.52 (m, 1H), 3.38–3.37 (m, 1H), 3.26 (s, 3H), 3.23–3.17 (m, 1H) 1.11 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 128.9, 115.5, 112.3, 75.6, 58.3, 47.0, 17.9.

*(S)-2-Ethyl-N-(1-methoxypropan-2-yl)-6-methylaniline (**6b**).*

Preparation of **6b** was similar to that of **6a**. Product **6b** (167.7 mg, 81% yield) was obtained from **5b** (392 mg, 1.0 mmol) as a colorless oil. In the scale up preparation, **6b** (30.7 g, 74% yield, GC 96%) was obtained by vacuum distillation (120 ^{o}C, 5 mm Hg); $[\alpha]_D^{20}$ = 10.6 (*c* = 1.40, $CHCl_3$). The ee value was determined by a chiral HPLC (Chiralcel OD column, hexane/*i*-PrOH = 99.5/0.5, flow rate 1.0 mL/min, λ = 254 nm, 99% ee: t_{major} = 5.5 min, t_{minor} = 5.1 min; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.26–7.01 (m, 2H), 6.90 (t, *J* = 7.5 Hz, 1H), 3.43–3.37 (m, 6H), 2.69 (q, *J* = 7.6 Hz, 2H), 2.33 (s, 3H), 1.30 (t, *J* = 7.6 Hz, 3H), 1.25–1.21 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 144.2, 135.4, 129.7, 128.6, 126.4, 121.6, 76.1, 58.9, 52.8, 24.1, 18.8, 18.4, 14.5.

*Methyl (2,6-dimethylphenyl)-L-alaninate (**6c**).*

Preparation of **6c** was similar to that of **6a**. Product **6c** (154.7 mg, 75% yield) was obtained from **6c** (392 mg, 1.0 mmol) as a colorless oil. In the scale up preparation, **6c** (29.8 g, 72% yield, GC 98%) was obtained by vacuum distillation (120 ^{o}C, 5 mm Hg); $[\alpha]_D^{20}$ = –0.5 (*c* = 0.61, $CHCl_3$);

dr = 71/29. The ee value was determined by a chiral HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 99.5/0.5, flow rate 1.0 mL/min, λ = 254 nm, 99% ee: t_{major} = 11.7 min, t_{minor} = 9.3 min; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.91 (d, J = 7.4 Hz, 2H), 6.72 (t, J = 7.4 Hz, 1H), 4.11 (d, J = 11.0 Hz, 1H), 3.91–3.80 (m, 1H), 3.56 (s, 3H), 2.22 (s, 6H), 1.33 (d, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.3, 144.3, 129.0, 128.7, 121.5, 54.8, 51.7, 19.1, 18.5.

(S)-2-chloro-N-(2-ethyl-6-methylphenyl)-N-(1-methoxypropan-2-yl)acetamide **(S-Metolachlor)**

The acylation of **6b** was prepared according to the reported procedures.[15] Crude (S)-Metolachlor (30.9 g, 90% yield, HPLC 94%) was obtained from **6b** (25.0 g, 0.12 mol) as a colorless oil. After distillation under vacuum (164–167 ^{o}C, 5 mmHg). Qualified (S)-Metolachlor (27.5 g, 80% yield, HPLC 98%) was obtained. $[\alpha]_D^{20}$ = 5.8 (c = 0.71, CH_2Cl_2). The ee value was determined by a chiral HPLC (Chiralcel OD+AS column, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer >99% ee: t_{major} = 28.2 min, t_{minor} = 33.5 min; minor diastereomer >99% ee: t_{major} = 27.1 min, t_{minor} = 43.8 min; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.26–7.09 (m, 3H), 4.20–4.18 (m, 1H), 3.73–3.63 (m, 1H), 3.58–3.57 (s, 2H, Major + Minor), 3.48–3.43 (m, 1H), 3.25–3.22 (s, 3H, Major + Minor), 2.58–2.52 (m, 2H), 2.22–2.20 (s, 3H, Major + Minor), 1.22 (t, J = 7.5 Hz, 3H), 1.14–1.10 (m, 3H). ^{13}C NMR (75 MHz, $CHCl_3$) δ 166.7, 142.5, 142.4, 137.1, 136.9, 136.8, 128.9, 128.8, 126.8, 126.7, 74.5, 58.5, 58.4, 55.3, 55.1, 42.8, 42.7, 23.8, 23.5, 18.82, 18.79, 15.4, 15.3, 14.1, 13.9.

Associated Content

Supporting Information

The spectra of intermediate and product are listed in the Supporting Information, which is available free of charge on the ACS Publications website.

Author Information

Corresponding Author

*E-mail: wlxioc@cioc.ac.cn.

Notes

The authors declare no competing financial interest.

References

1. (a) Guizzetti, S.; Benaglia, M.; Cozzi, F.; Annunziata, R. *Tetrahedron* **2009**, *65*, 6354; (b) Li, Q.; Hou, C. J.; Liu, X. N.; Huang, D. Z.; Liu, Y. J.; Yang, R. F.; Hu, X. P. *RSC Adv.* **2015**, *5*, 13702; (c) Hou, C. J.; Wang, Y. H.; Zheng, Z.; Xu, J.; Hu, X. P. *Org. Lett.* **2012**, *14*, 3554; (d) Blaser, H. U.; Buser, H. P.; Hausel, R.; Jalett, H. P.; Spindler, F. *J. Organomet. Chem* **2001**, *621*, 34; (e) Loch, A. R.; Lippa, K. A.; Carlson, D. L.; Chin, Y. P.; Traina, S. J.; Roberts, A. L. *Environ. Sci. Technol.* **2002**, *36*, 4065 ; (f) Tang, W.; Johnston, S.; Li, C.; Iggo, J. A.; Bacsa, J.; Xiao, J. *Chemistry* **2013**, *19*, 14187; (g) Dorta, R.; Broggini, D.; Stoop, R.; Ruegger, H.; Spindler, F.; Togni, A. *Chemistry* **2004**, *10*, 267; (h) Goulden, P. H.; Coffinet, S.; Genty, C.; Bourcier, S.; Sablier, M.; Bouchonnet, S. *Anal. Chem.* **2011**, *83*, 7587; (i) Busacca, C. A.; Fandrick, D. R.; Song, J. J.; Senanayake, C. H. *Adv. Synth. Catal.* **2011**, *353*, 1825.

2. (a) Hou, C. J.; Wang, Y. H.; Zheng, Z.; Xu, J.; Hu, X. P. *Org. Lett.* **2012**, *14*, 3554; (b) Blaser, H.-U. *Adv. Synth. Catal.* **2002**, *344*, 17 ; (c) Spindler, V. F.; Pugin, B.; Blaser, H.-U. *Angew. Chem.* **1990**, *102*, 561 ; (d) Saaby, S.; Winckelmann, I.; Sondergaard, K.; Liang, X.; Ke, Y.; Wang, X.; Ye, J. Process for the hydrogenation of imines. U.S Pat. Appl. 20110077418 A1, 2011; (e) Li, J. Catalyst for Asymmetric Hydrogenation of Imine, Synthesis Method and Application Thereof. U.S Pat. Appl. 20140018548 A1, 2014.

3. (a) Liu, D.; Maguire, R. J.; Pacepavicius, G. J. *environ. Toxicol. Water Qual.* **1995**, *10*, 249 ; (b) Krause, A.; Hancock, W. G.; Minard, R. D.; Freyer, A. J.; Honeycutt, R. C.; LeBaron, H. M.; Paulson, D. L.; Liu, S. Y.; Bollag, J. M. *J. Agric. Food Chem.* **1985**, *33*, 584.

4. (a) Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1992**, *3*, 337 ; (b) Brunel, J. M.; Buono, G. *Synlett.* **1995**, 177.

5. Zhu, H.; Li, Y.; Chen, W.; Yu, G.; Du, G.; Lv, L.; Chu, Q. A novel method for the synthesis of (S)-Metolachlor. Chinese Patent CN 101367746 A, 2009.

6. (a) Liu, L. W.; Wang, F. Y.; Tian, F.; Peng, L.; Wang, L. X. *Org. Process Res. Dev.* **2016**, *20*, 320; (b) Wang, F.; Xu, X. Y.; Wang, F. Y.; Peng, L.; Zhang, Y.; Tian, F.; Wang, L. X. *Org. Process Res. Dev.* **2013**, *17*, 1458; (c) Huang, J.; Wang, W.; Wang, L. X. *Org. Process Res. Dev.* **2010**, *14*, 1464; (d) Wang, L.; Shen, J.; Tang, Y.; Wang, W.; Cai, Z.; Du, Z. *Org. Process Res. Dev.* **2007**, *11*, 487.

7. (a) Wang, L. X.; Tang, Y.; Chen, Y.; Tian, F. Preparation of Clopidogrel and its analogues methyl tetrahydrothienopyridine acetate compounds. Eur. Pat. Appl. 1942110A1, 2008. (b)

Wang, L. X.; Tang, Y.; Chen, Y.; Tian, F. Preparation of Clopidogrel and its analogues methyl tetrahydrothienopyridine acetate compounds. WO Pat. Appl. 2007/028337 A1, 2007. (c) Wang, L. X.; Tang, Y.; Chen, Y.; Tian, F. Preparation of Clopidogrel and its analogues methyl tetrahydrothienopyridine acetate compounds. U.S. Pat. Appl. 2008/249311 A1, 2008.

8. (a) Wang, L. X.; Peng, L.; Qin, B.; Wang, W.; Tian, F.; Huang, Q.-C.; He, G.-Y. Preparation of Aliskiren intermediate derivatives 3-isopropyl-2-(5H)-furanone. Chinese Patent CN 201310030823. 4, 2013. (b) Wang, L. X.; Zhang, C. J; Wang, F. Y.; Zhi, Y. G.; Tian, F.; He, G. Y. Preparation of furanone intermediate derivatives of Aliskiren--a kind of antihypertensive drug. Chinese Patent CN 201310030835. 7, 2013. (c) Wang, L. X.; Yang, P.; Wang, X.; Peng, L.; A Novel Preparation of (S)-Metolachlor and its analogs. Chinese Patent 201710024322.3, 2017. (d) Wang, L. X.; Yang, P.; Wang, X.; Peng, L.; A Novel Preparation of (S)-Metolachlor intermediate derivatives. Chinese Patent 201710024324.2, 2017.

9. (a) Fukuyama, T.; Jow, C. K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373 ; (b) Fukuyama, T.; Cheung, M.; Jow, C. K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831. (c) Tyagi, S.; Gichinga, M. G.; Cook, C. D.; Key, J. A.; McKillican, B. P.; Eberle, W. J.; Carlin, T. J.; Hunt, D. A.; Dowling, A. J. *Tetrahedron Lett.* **2016,** *57*, 5363.

10. (a) Ingleson, M. J.; Barrio, J. P.; Bacsa, J.; Dickinson, C.; Park, H.; Rosseinsky, M. J. *Chem Commun (Camb)* **2008**, 1287; (b) Liang, S.; Zhou, Y.; Liu, H.; Jiang, T.; Han, B. *Synth. Commun.* **2011**, *41*, 891; (c) Zhang, Y.; Lu, B.; Wang, X.; Zhao, J.; Cai, Q. *Applied Catalysis A: General* **2011**, *408*, 125; (d) Pautard, A. M.; Evans, S. A.; Jr. *J. Org. Chem.* **1988**, *53*, 2300.

11. (a) Le Pera, A.; Leggio, A.; Liguori, A. *Tetrahedron* **2006**, *62*, 6100; (b) Yrjola, S.; Parkkari, T.; Navia-Paldanius, D.; Laitinen, T.; Kaczor, A. A.; Kokkola, T.; Adusei-Mensah, F.; Savinainen, J. R.; Laitinen, J. T.; Poso, A.; Alexander, A.; Penman, J.; Stott, L.; Anskat, M.; Irving, A. J.; Nevalainen, T. J. *Eur. J. Med. Chem.* **2016**, *107*, 119.

12. Okano, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 4987.

13. (a) MacMillan, K. S.; Naidoo, J.; Liang, J.; Melito, L.; Williams, N. S.; Morlock, L.; Huntington, P. J.; Estill, S. J.; Longgood, J.; Becker, G. L.; McKnight, S. L.; Pieper, A. A.; De Brabander, J. K.; Ready, J. M. *J. Amer. Chem. Soc.* **2011**, *133*, 1428; (b) Kurkin, A. V.; Bernovskaya, A. A.; Yurovskaya, M. A. *Tetrahedron: Asymmetry* **2009**, *20*, 1500.

14. The reactions are almost occurred quantitatively in every step, while restricted by the quantity of the product and the distillation apparatus in laboratory scale,the sepatated yields are resonably lowered than the detected yields.

15. Wen, P. H.; Liang, J. F.; Chen, G. B.; Feng, Y. J.; Chen, J. K.; Chen, J. Y.; Mei, X. L.; Shen, H. W.; Sun, J. S.; Hu, W. Q.; Lv, H.; Xu, J. P.; Wang, M., Total synthesis of metolachlor. Chinese Patent 2016, CN105461580.

16. Park, O. J.; Lee, S. H.; Park, T. Y.; Lee, S. W.; Cho, K.-H. *Tetrahedron: Asymmetry* **2005**, *16*, 1221.

17. Bosone, E.; Camaggi, G.; Lodi; Vries, L. d.; Garavaglia, C.; Garlaschelli, L.; Gozzo, F.; Overeem, J. C.; Lorusso, S. Acyl anilines exerting a fungicidal action. U.S Pat. Appl. 4291049, 1981.

18. Eisenmann, J.; Yamartino, R.; Howard, J. J. *J. Org. Chem.* **1961**, 26, 2102.

Graphic for manuscript