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Regio- and Diastereoselective Construction of α-Hydroxy-δ-amino Ester Derivatives via 1,4-Conjugate Addition of β,γ-Unsaturated *N*-Sulfonylimines

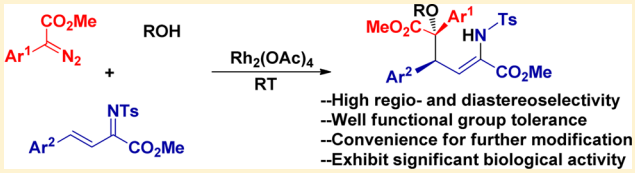
Lin Qiu,[†] Lixin Gao,[‡] Jixing Tang,[†] Dongwei Wang,[†] Xin Guo,[†] Shunying Liu,*[,†] Liping Yang,[†] Jia Li,[†,‡] and Wenhao Hu*[,†]

[†]Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, Department of Chemistry, East China Normal University, Shanghai, 200062, China

[‡]National Center for Drug Screening, State Key Laboratory of Drug Research,Shanghai Institute of MateriaMedica, Chinese Academy of Science, Shanghai, 201203, China

Supporting Information

ABSTRACT: A first example of 1,4-conjugate addition of β,γ-unsaturated *N*-sulfonylimines via the oxonium ylides trapping process was developed. This method afforded a novel and efficient access for the high regio- and diastereoselective construction of α-hydroxyl-δ-amino esters derivatives, which exhibit inhibitory activity on PTP1B and SIRT1 enzymes in vitro. The synthetic potentials and the biological activity of the resulting products were well demonstrated to be promising for drug discovery.



Conjugate addition is one of the most general and versatile methods for carbon chain growth and complex molecule construction in organic synthesis.[1] Unsaturated carbonyl compounds,[2] nitroalkenes[3] and unsaturated sulfones[4] have commonly served as electrophilic counterpartners to participate in the conjugate addition reactions. Compared to the above-mentioned electrophiles, β,γ-unsaturated imines (1-azabutenes), which demonstrated as versatile synthetic building blocks in cycloaddition reactions,[5] have been limited to be explored yet in conjugate addition reaction likely due to their lower electrophilicity.[6] Thus, it has given impetus to the development of new access to conjugate addition reactions of β,γ-unsaturated imines.

As ambident electrophiles, β,γ-unsaturated imines can either undergo 1,2- or 1,4-nucleophilic addition processes, so it is more challenging for the nucleophilic addition to control the regioselectivity, which strongly relies on the nucleophiles and catalytic reagents. The 1, 2-addition processes were often preferred in nucleophilic addition reactions.[7] However, only a few examples have been reported on the 1,4-conjugate addition involving β,γ-unsaturated imines.[8] Carretero and co-workers developed copper-catalyzed enantioselective 1,4-conjugate addition of dialkyl zinc to β,γ-unsaturated imines to synthesize the alkylated products.[8b] Leung's group also demonstrated a protocol for the asymmetric 1,4-addition of Ph_2PH to β,γ-unsaturated ketimines catalyzed by palladacycle.[8d] Very recently, Pedro and co-workers developed the first enantioselective 1,4-conjugate addition of dimethyl malonate to β,γ-unsaturated *N*-tosylimines catalyzed by PyBOX/$La(OTf)_3$ complexes.[8e] But to our knowledge, nucleophilic addition of active oxonium ylides to β,γ-unsaturated imines has never been accessed. The conjugate addition of β,γ-unsaturated *N*-sulfonylimines via the oxonium ylides trapping process offer a multicomponent strategy[9] to install complex compounds with a step-economical fashion.

In the past few years, we have successfully developed multicomponent active intermediate reactions,[10] especially oxonium ylides[10a−h] as nucleophiles to furnish highly stereoselective 1,4-conjugate addition to α,β-unsaturated 2-acylimidazoles[10e] and chalcone[10g] via the trapping process. In connection with our continuous interest, here we describe the first example of highly regio- and diasteroselective 1,4-conjugate addition of oxonium ylides to β,γ-unsaturated *N*-tosylimines. The efficient procedure provides an easy access to α-hydroxyl-δ-amino esters derivatives, which are valuable synthetic building blocks in organic chemistry[11] and promising for drug discovery owing to their versatile functionalities.

With the conditions established in previous work, we began our studies with the reaction of methyl phenyldiazoacetate **1a**, benzyl alcohol **2a**, and Ts-protected β,γ-unsaturated imines **3a** in the presence of 1 mol % of $Rh_2(OAc)_4$ in CH_2Cl_2 at room temperature. Fortunately, ketimine **3a** bearing an ester substituent at the α-position was found to be more 1,4-selective to give the desired conjugated addition product γ-dehydro-α-hydroxyl-δ-amino esters derivatives (enamines) with >95:5 dr in 45% yield. Interestingly, the double bond of all the enamines **5a** had (*Z*)-geometry, and the addition occurred with 1,4-regioselectivity. With the addition of 4 Å molecular sieve (MS), the yield was increased up to 65%, and the

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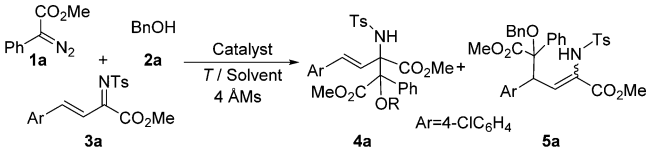
diastereomeric ratio was maintained as >95:5 (Table 1, entry 1). Encouraged by this result, we further optimized the reaction

Table 1. Optimization of Reaction Conditions for the Reaction of 1a, 2a, and 3a[a]



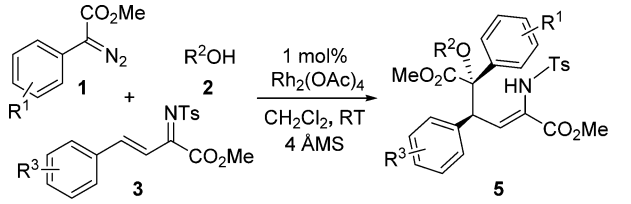
entry	solvent	T (°C)	catalyst (mol %)	yield[b] (%)	dr[c]
1	CH_2Cl_2	25	$Rh_2(OAc)_4$ (1)	65	>95:5
2	toluene	25	$Rh_2(OAc)_4$ (1)	56	>95:5
3	$(ClCH_2)_2$	25	$Rh_2(OAc)_4$ (1)	50	>95:5
4	$CHCl_3$	25	$Rh_2(OAc)_4$ (1)	43	>95:5
5	THF	25	$Rh_2(OAc)_4$ (1)	<5	
6	CH_2Cl_2	−20	$Rh_2(OAc)_4$ (1)	64	>95:5
7	CH_2Cl_2	0	$Rh_2(OAc)_4$ (1)	60	>95:5
8	CH_2Cl_2	40	$Rh_2(OAc)_4$ (1)	35	>95:5
9	CH_2Cl_2	40	$Cu(OTf)_2$ (10)	43	>95:5
10	CH_2Cl_2	40	Cu(OTf) (10)	45	>95:5

[a]Reaction conditions: unless otherwise noted, the reaction was carried out with **1a**:**2a**:**3a** = 1.2:1.5:1.0. [b]Isolated yield of **5a** based on **3a**. [c]Determined by ^{1}H NMR analysis.

conditions, and the results were summarized in Table 1. The solvents had a significant effect on the product yields (Table 1, entries 2−5). CH_2Cl_2 was demonstrated as a better solvent than toluene, 1,2-dichloroethane, and chloroform (Table 1, entries 2−4). THF only afforded trace amounts of the desired product (Table 1, entry 5). The evaluation of the reaction temperature showed that room temperature was the optimal temperature. Lowering the temperature to −20 °C had no notable effect on the product yield (Table 1, entries 6 and 7), but higher temperature led to a sharp decrease in yield from 65% to 35% (Table 1, entry 8 vs 1). It was found that $Cu(OTf)_2$ and Cu(OTf) also gave the desired product **5a** in 43% and 45% yield at 40 °C (Table 1, entries 9 and 10). Finally, the optimized condition was defined as at 25 °C in CH_2Cl_2 with 4 Å molecular sieves (MS) as additive, and the desired product **5a** was given in 65% yield with >95:5 dr (Table 1, entry 1).

With the set of the standard conditions, we then proceeded to investigate the reaction scope. The results are tabulated in Table 2. Varying the electronic feature of the phenyl ring in diazo compounds had a positive effect on the yield (Table 2, entries 1−5). Both the electron-donating and electron-withdrawing substituents at 3- or 4-position of the phenyl group afforded the corresponding product in good to excellent yields (83−90%) with a high level of diastereoselective control. Benzyl alcohols **2** bearing a 4-methoxyl or halogen substitutent gave no desired products except O−H insertion byproducts (Table 2, entries 6 and 7). Regardless of steric effect, both 2- and 4-nitro-substituted benzyl alcohols **2e** and **2f** gave corresponding products in similarly good yield with excellent dr (Table 2, entries 8 and 9). These results indicated that, for benzyl alcohols, the electronic effect had a notable influence on the reactivity of the resulting oxonium ylides. Gratifyingly, alkyl alcohols were well tolerant to this three-component reaction (Table 2, entries 10−12). For example, isopropyl alcohol **2g** gave the corresponding product **5i** in the highest yield (95%) and excellent diastereoselectivity (>95:5) (Table 2, entry 10).

Table 2. Substrate Scope of Three-Component Reactions[a]



entry	R^1	R^2	R^3	5	yield[b] (%)	dr[c]
1	4-MeO (**1b**)	Bn (**2a**)	4-Cl (**3a**)	**5b**	90	>95:5
2	4-Me (**1c**)	Bn (**2a**)	4-Cl (**3a**)	**5c**	85	>95:5
3	4-Br (**1d**)	Bn (**2a**)	4-Cl (**3a**)	**5d**	85	>95:5
4	3-Br (**1e**)	Bn (**2a**)	4-Cl (**3a**)	**5e**	83	>95:5
5	4-Cl (**1f**)	Bn (**2a**)	4-Cl (**3a**)	**5f**	84	>95:5
6	H (**1a**)	4-$BrC_6H_4CH_2$ (**2c**)	4-Cl (**3a**)		<5	
7	H (**1a**)	4-$MeOC_6H_4CH_2$ (**2d**)	4-Cl (**3a**)		<5	
8	H (**1a**)	2-$NO_2C_6H_4CH_2$ (**2e**)	4-Cl (**3a**)	**5g**	56	>95:5
9	H (**1a**)	4-$NO_2C_6H_4CH_2$ (**2f**)	4-Cl (**3a**)	**5h**	64	>95:5
10	H (**1a**)	^{i}Pr (**2g**)	4-Cl (**3a**)	**5i**	95	>95:5
11	H (**1a**)	Et (**2h**)	4-Cl (**3a**)	**5j**	82	>95:5
12	H (**1a**)	Me (**2i**)	4-Cl (**3a**)	**5k**	75	>95:5
13	H (**1a**)	Bn (**2a**)	4-Me (**3b**)	**5l**	56	>95:5
14	H (**1a**)	Bn (**2a**)	4-Br (**3c**)	**5m**	68	>95:5
15	H (**1a**)	Bn (**2a**)	3-Br (**3d**)	**5n**	63	>95:5
16	H (**1a**)	Bn (**2a**)	4-F (**3e**)	**5o**	78	>95:5
17	H (**1a**)	Bn (**2a**)	H (**3f**)	**5p**	57	>95:5
18	H (**1a**)	Bn (**2a**)	4-NO_2 (**3g**)	**5q**	64	>95:5
19	H (**1a**)	TSE[d] (**2j**)	H (**3f**)	**5r**	70	>95:5

[a]For conditions: unless otherwise noted, the reaction was carry out with **1a**:**2a**:**3a** = 1.2:1.5:1.0, catalyzed by 1 mol % of $Rh_2(OAc)_4$. [b]Isolated yield of **5** based on **3**. [c]Determined by ^{1}H NMR spectroscopy. [d]TSE = 2-(trimethylsilyl)ethyl.

The current three-component reactions are also applicable when *β,γ*-unsaturated imines with various electronic properties were used. Good yields (56−78%) and excellent diastereoselectivities (>95:5) were obtained with substrates bearing either electron-withdrawing or -donating groups on the aryl rings of *β,γ*-unsaturated imines (Table 2, entries 13−18). 2-(Trimethylsilyl)ethanol (**2j**) also gave a good result when *β,γ*-unsaturated imine **3f** was used (Table 2, entry 19). Notably, it seemed that the ester group at *α*-position in unsaturated imines was indispensable for the current reaction (Supporting Information, Scheme S2).

In the conjugate addition pathway, we proposed an intermolecular hydrogen bond in intermediate **B** is the key aspect accounting for the diastereoselective control (Scheme 1 and Scheme S1, Supporting Information). Intermediate **B** rather than **A** would be eventually transformed into the favored *Z-anti*-product as the major product. The relative stereochemistry of products was assigned in analogy with *Z-anti*-**5g** whose structure was determined by single-crystal X-ray diffraction (Supporting Information).

The resulting three-component products **5** were demonstrated as synthetically valuable motifs (Scheme 2). For

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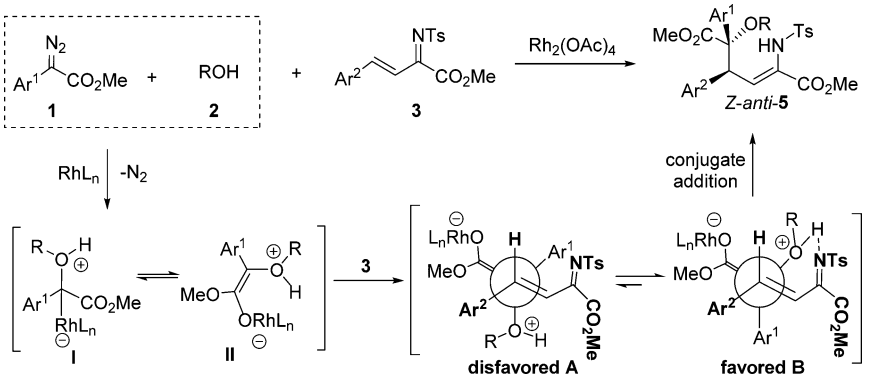
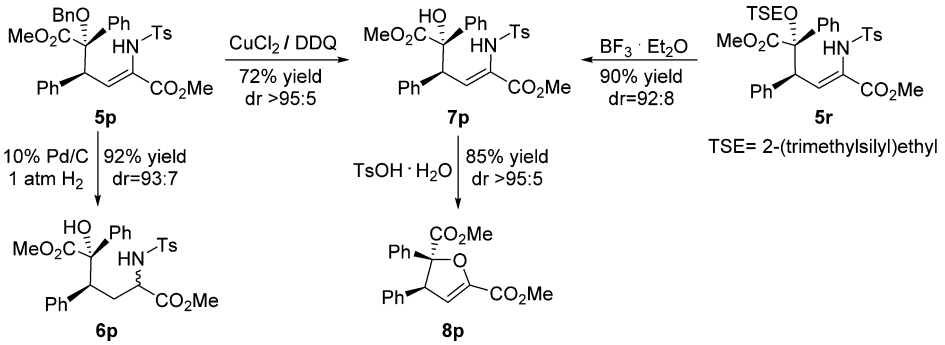
Scheme 1. Possible Mechanism for the Three-Component Reaction



Scheme 2. Synthetic Application of the Product



example, **5p** was hydrogenated into the corresponding saturated adipic acid ester **6p** in 92% yield with 93:7 dr value. Cleavage of the benzyl auxiliary from the enamine product **5p** was accomplished using an oxidation process with $CuCl_2$/DDQ, which provided the free hydroxyl compound **7p** in 72% yield. Meanwhile, removal of TSE protection in **5r** can be easily achieved to give **7p** in the presence of trifluoroborane in high yield with conservation of the diastereoselectivity (92:8 dr). Furthermore, treatment of **7p** with *p*-toluenesulfonic acid under reflux in toluene afforded 2,3-dihydrofuran derivative **8p** in 85% yield with >95:5 dr value.

The value of our practically synthesized compounds has been demonstrated in exploring biological activity against both PTP1B and SIRT1 targets. PTP1B have been shown to play a major role in the dephosphorylation of the insulin receptor in many cellular and biochemical studies. Therefore, biologically active PTP1B inhibitors could be potential pharmacological agents for the treatment of Type-II diabetes and obesity.[12] SIRT1 has the most characterized sirtuin members (SIRT1−SIRT7) in the histone deacetylase (HDACa) family that are considered potential targets for metabolic, inflammatory, oncologic, and neurodegenerative disorders.[13] To our delight, in a bioassay in vitro, the preliminary resulting products **5** bearing *γ*-dehydro-*α*-hydroxy-*δ*-amino esters derivatives scaffold exhibited significant inhibitory activity against both PTP1B and SIRT1 with IC_{50} values in the low micromolar range for several compounds (Table 3 and Table S1, Supporting Information). The promising results suggest that the biologically active scaffold is worthy for additional structure activity relationship (SAR) study.

In summary, we have successfully developed a protocol for the multicomponent 1,4-conjugate reaction of *β*,*γ*-unsaturated imines via the oxonium ylide trapping process. This provided an efficient access to build *γ*-dehydro-*α*-hydroxyl-*δ*-amino esters derivatives in moderate to high yields with excellent regio- and diastereoselectivities under mild reaction conditions. The synthetic potentials of the prepared *γ*-dehydro-*α*-hydroxyl-*δ*-amino esters derivatives were demonstrated. The initially biological investigation revealed the products **5** could be a potential novel class of PTP1B and SIRT1 inhibitors.

Table 3. Inhibitory Activity of Compounds 5 against PTP1B and SIRT1

entry	5	PTP1B (inhibition %)[a]	PTP1B IC_{50} (μM)[a]	SIRT1 (inhibition %)[b]	SIRT1 IC_{50}[b] (μM)
1	**5c**	96.5 ± 0.2	5.4 ± 0.8	66.0 ± 9.2	14.3 ± 4.0
2	**5d**	58.1 ± 6.1	17.8 ± 2.6	19.9 ± 3.9	ND[c]
3	**5j**	95.0 ± 1.6	1.6 ± 0.1	39.9 ± 8.4	ND[c]
4	**5k**	2.7 ± 4.9	ND[c]	68.8 ± 4.0	15.6 ± 1.7
5	**5l**	92.2 ± 2.2	2.2 ± 0.2	44.7 ± 7.5	ND[c]

[a]Inhibition of PTP1B produced by the tested compounds at 20 μg/mL. [b]Inhibition of SIRT1 produced by the tested compounds at 20 μg/mL. [c]ND: the IC_{50} of compounds were not determined since the inhibition rate at 20 μg/mL was lower than 50%.

EXPERIMENTAL SECTION

General Methods. All moisture sensitive reactions were performed under an argon atmosphere in a well-dried reaction flask. Dichloromethane (CH_2Cl_2), 1,2-dichloroethene [$(CH_2Cl)_2$] and chloroform ($CHCl_3$) were freshly distilled over calcium hydride, toluene from sodium benzophenoneketyl, respectively, prior to use. All commercially available reagents were directly used as received from vendors, unless otherwise stated. Chemical shifts (δ value) were reported in ppm downfield from internal tetramethylsilane (TMS). Chemical shifts were reported in parts per million as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet).

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General procedure for the three-component reaction. To a stirred solution of $Rh_2(OAc)_4$ (0.002 mmol), alcohols **2** (0.30 mmol), *β*,*γ*-unsaturated *N*-sulfonylimines **3** (0.20 mmol) and 100 mg 4 Å MS in dichloromethane (1.5 mL) at room temperature for 10 min, then added diazo compounds **1** (0.24 mmol) in dichloromethane (0.5 mL) over 1 h. After completion of the addition, the reaction mixture was stirred for another 1 h. Solvent was removed, and a portion of crude product was subjected to ^{1}H NMR analysis for determination of diastereoselectivity. The crude product was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether =1:10−1:3) to give the corresponding products **5**.

*(Z)-Dimethyl 5-(benzyloxy)-4-(4-chlorophenyl)-2-(4-methylphenylsulfonamido)-5- phenylhex-2-enedioate (**5a**).* Amorphous powder, yield: 65%, dr: >95:5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 3.49 (s, 3H), 3.76 (s, 3H), 4.34 (d, J = 9.2 Hz, 1H), 4.64 (d, J = 9.6 Hz, 1H), 4.87 (d, J = 8.4 Hz, 1H), 6.26 (s, 1H), 6.93 (d, J = 6.8 Hz, 2H), 7.13 (m, 4H), 7.26 (m, 6H), 7.30 (m, 3H), 7.34 (m, 2H), 7.47 (d, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 52.2, 52.5, 52.7, 63.1, 88.3, 125.7, 126.9, 127.4, 127.5, 127.8, 127.8, 128.3, 128.3, 129.2, 131.7, 133.1, 135.1, 135.4, 136.0, 138.2, 138.9, 143.7, 164.5, 171.3; HRMS (ESI): Calcd for $C_{34}H_{32}ClNNaO_7S$, $[M + Na]^+$: 656.1480; Found: 656.1470.

*(Z)-Dimethyl 5-(benzyloxy)-4-(4-chlorophenyl)-5-(4-methoxyphenyl)-2-(4-methyl- phenylsulfonamido) hex-2-enedioate (**5b**).* Amorphous powder, yield: 90%, dr: >95:5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.49 (s, 3H), 3.74 (s, 3H), 3.78 (s, 3H), 4.28 (d, J = 11.7 Hz, 1H), 4.59 (d, J = 11.7 Hz, 1H), 4.83 (d, J = 10.6 Hz, 1H), 6.31 (s, 1H), 6.77 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.2 Hz, 2H), 7.13(m, 6H), 7.27(m, 7H), 7.45(d, J = 11.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 52.2, 52.9, 52.2, 55.2, 68.0, 88.2, 113.2, 125.9, 127.0, 127.4, 127.4, 127.6, 128.3, 129.3, 129.3, 131.8, 133.1, 135.3, 136.2, 138.4, 138.9, 143.7, 159.4, 164.6, 171.6; HRMS (ESI): Calcd for $C_{35}H_{34}ClNNaO_8S$, $[M + Na]^+$: 686.1586; Found: 686.1582.

*(Z)-Dimethyl 5-(benzyloxy)-4-(4-chlorophenyl)-2-(4-methylphenylsulfonamido)-5- p-tolylhex-2-enedioate (**5c**).* Colorless solid, mp: 134−135 °C, yield: 85%, dr: >95:5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H), 2.36 (s, 3H), 3.50 (s, 3H), 3.75 (s, 3H), 4.34 (d, J = 9.2 Hz, 1H), 4.60 (d, J = 9.2 Hz, 1H), 4.83 (d, J = 8.4 Hz, 1H), 6.29 (s, 1H), 6.93 (d, J = 6.4 Hz, 2H), 7.06 (m, 4H), 7.13 (m, 4H), 7.25 (m, 1H), 7.30 (m, 3H), 7.35 (m, 2H), 7.46 (d, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 21.4, 52.2, 52.5, 52.7, 68.0, 88.3, 125.8, 127.0, 127.3, 127.4, 127.6, 127.8, 128.3, 128.5, 129.2, 131.7, 132.3, 133.0, 135.2, 138.2, 138.3, 138.8, 143.6, 164.5, 171.5; HRMS (ESI): Calcd for $C_{35}H_{34}ClNNaO_7S$, $[M + Na]^+$: 670.1637; Found: 670.1609.

*(Z)-Dimethyl5-(benzyloxy)-5-(4-bromophenyl)-4-(4-chlorophenyl)-2-(4-methyl-phenylsulfonamido) hex-2-enedioate (**5d**).* Amorphous powder, yield: 85%, dr: >95:5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 3.51 (s, 3H), 3.78 (s, 3H), 4.29 (d, J = 11.6 Hz, 1H), 4.63(d, J = 11.6 Hz, 1H), 4.91 (d, J = 10.8 Hz, 1H), 6.24 (s, 1H), 6.96 (d, J = 8.8 Hz, 2H), 7.15 (m, 6H),7.28 (m, 2H), 7.33 (m, 3H), 7.39 (m, 4H), 7.47 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 52.4, 52.5, 52.7, 68.3, 87.9, 122.6, 125.9, 127.0, 127.4, 127.6, 127.8, 128.4, 129.3, 129.7, 131.0, 131.7, 133.4, 134.7, 134.9, 136.0, 137.9, 138.5, 143.8, 164.3, 170.9; HRMS (ESI): Calcd for $C_{34}H_{31}BrClNNaO_7S$, $[M + Na]^+$: 734.0585; Found: 734.0576.

*(Z)-Dimethyl5-(benzyloxy)-5-(3-bromophenyl)-4-(4-chlorophenyl)-2-(4-methyl-phenyl-sulfonamido) hex-2-enedioate (**5e**).* Amorphous powder, yield: 83%, dr: >95:5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37(s, 3H), 3.50 (s, 3H), 3.77 (s, 3H), 4.29 (d, J = 9.6 Hz, 1H), 4.63 (d, J = 9.2 Hz, 1H), 4.86 (d, J = 8.4 Hz, 1H), 6.22 (s, 1H), 6.93 (d, J = 6.8 Hz, 2H), 7.15 (m, 6H), 7.28 (m, 2H), 7.33 (m, 3H), 7.39 (m, 4H), 7.47 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 52.4, 52.6, 52.7, 68.4, 87.8, 122.0, 125.9, 126.5, 127.1, 127.4, 127.6, 127.7, 128.4, 129.2, 131.0, 131.4, 131.6, 133.4, 134.8, 137.8, 137.9, 138.3, 143.8, 164.3, 170.8; HRMS (ESI): Calcd for $C_{34}H_{31}BrClNNaO_7S$, $[M + Na]^+$: 734.0585; Found: 734.0610.

*(Z)-Dimethyl5-(benzyloxy)-4,5-bis(4-chlorophenyl)-2-(4-methyl-phenyl-sulfon-amido)hex-2-enedioate (**5f**).* Amorphous powder, yield: 84%, dr: >95:5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 3.51 (s, 3H), 3.78 (s, 3H), 4.31 (d, J = 11.6 Hz, 1H), 4.63 (d, J = 11.6 Hz, 1H), 4.91 (d, J = 10.8 Hz, 1H), 6.25 (s, 1H), 6.96 (d, J = 8.4 Hz, 2H), 7.15 (m, 6H), 7.28 (m, 2H), 7.33 (m, 3H), 7.39 (m, 4H), 7.48 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 52.4, 52.5, 52.7, 53.4, 68.3, 87.9, 126.0, 127.0, 127.4, 127.6, 127.7, 128.0, 128.4, 129.3, 129.4, 131.7, 133.3, 134.2, 134.3, 135.0, 136.1, 137.9, 138.5, 143.8, 164.4, 171.0; HRMS (ESI): Calcd for $C_{34}H_{31}Cl_2NNaO_7S$, $[M + Na]^+$: 690.1090; Found: 690.1056.

*(Z)-Dimethyl 5-(2-nitrobenzyloxy)-4-(4-chlorophenyl)-2-(4-methylphenyl-sulfon- amido)-5-phenylhex-2- enedioate (**5g**).* Colorless solid, mp: 165−166 °C, yield: 56%, dr: >95:5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 3H), 3.37 (s, 3H), 3.62 (s, 3H), 4.60 (d, J = 15.1 Hz, 1H), 4.90 (dd, J = 12.8, 7.6 Hz, 2H), 6.09 (s, 1H), 7.40−6.99 (m, 15H), 7.57 (t, J = 7.6 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 52.3, 52.6, 53.1, 65.3, 88.9, 124.5, 125.8, 126.4, 127.4, 127.6, 127.7, 127.8, 128.2, 128.7, 129.3, 129.6, 131.7, 133.2, 133.6, 135.0, 135.3, 135.4, 135.8, 138.9, 143.9, 147.0, 164.4, 171.1; HRMS (ESI): Calcd for $C_{34}H_{31}ClN_2NaO_9S$, $[M + Na]^+$: 701.1331; Found: 701.1331.

*(Z)-Dimethyl 5-(4-nitrobenzyloxy)-4-(4-chlorophenyl)-2-(4-methylphenyl-sulfon- amido)-5-phenylhex-2-enedioate (**5h**).* Amorphous powder, yield: 64%, dr: >95:5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.46 (s, 3H), 3.76 (s, 3H), 4.36 (d, J = 13.3 Hz, 1H), 4.73 (d, J = 13.3 Hz, 1H), 5.02 (d, J = 10.7 Hz, 1H), 6.17 (s, 1H), 7.04 (d, J = 7.8 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 7.7 Hz, 1H), 7.48−7.21 (m, 4H), 8.18 (d, J = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 52.3, 52.6, 52.8, 67.3, 88.7, 123.5, 125.8, 126.4, 127.3, 127.4, 127.7, 128.2, 128.8, 129.3, 129.6, 131.7, 133.3, 135.3, 135.3, 135.7, 138.8, 143.9, 146.1, 147.1, 164.3, 171.1; HRMS (ESI): Calcd for $C_{34}H_{31}ClN_2NaO_9S$, $[M + Na]^+$: 701.1331; Found: 701.1351.

*(Z)-Dimethyl 4-(4-chlorophenyl)-5-isopropoxy-2-(4-methylphenylsulfonamido)-5- phenylhex-2-enedioate (**5i**).* Amorphous powder, yield: 95%, dr: >95:5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (d, J = 6 Hz, 3H), 1.17 (d, J = 6 Hz, 3H), 2.42 (s, 3H), 3.54 (s, 3H), 3.72 (s, 3H), 3.86 (m, 1H), 4.76 (d, J = 10 Hz, 1H), 6.82 (d, J = 8.8 Hz, 2H), 7.10 (m, 4H), 7.24 (m, 5H), 7.59 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 23.4, 23.9, 51.8, 51.9, 52.5, 69.5, 88.0, 126.1, 127.4, 127.5, 128.2, 128.3, 129.3, 131.7, 133.0, 135.6, 136.5, 136.8, 139.3, 143.7, 164.7, 171.6; HRMS (ESI): Calcd for $C_{30}H_{32}ClNNaO_7S$, $[M + Na]^+$: 608.1480; Found: 608.1455.

*(Z)-Dimethyl 4-(4-chlorophenyl)-5-ethoxy-2-(4-methylphenylsulfonamido)-5- phenyl-hex-2-enedioate (**5j**).* Colorless solid, mp: 148−149 °C, yield: 82%, dr: >95:5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (dd, J = 12.8, 5.9 Hz, 3H), 2.37 (s, 3H), 3.40−3.21 (m, 1H), 3.52 (s, 3H), 3.57 (m, 1H), 3.75 (s, 3H), 4.65 (d, J = 10.6 Hz, 1H), 6.49 (s, 1H), 6.83 (d, J = 7.7 Hz, 2H), 7.13−7.02 (m, 4H), 7.23−7.13 (m, 6H), 7.54 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.4, 21.5, 52.2, 52.5, 52.6, 62.0, 88.1, 125.9, 127.4, 127.6, 127.6, 127.6, 128.1, 129.3, 131.6, 133.0, 135.2, 135.8, 136.3, 138.9, 143.7, 164.7, 171.6; HRMS (ESI): Calcd for $C_{29}H_{30}ClNNaO_7S$, $[M + Na]^+$: 594.1324; Found: 594.1315

*(Z)-Dimethyl 4-(4-chlorophenyl)-5-methoxy-2-(4-methylphenylsulfonamido)-5- phenyl-hex-2-enedioate (**5k**).* Amorphous powder, yield: 75%; dr: >95:5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 3.28 (s, 3H), 3.51 (s, 3H), 3.77 (s, 3H), 4.71 (d, J = 10.6 Hz, 1H), 6.33 (s, 1H), 6.85 (d, J = 7.7 Hz, 2H), 7.13−7.02 (m, 6H), 7.26−7.12 (m, 4H), 7.50 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 52.2, 52.5, 52.5, 54.6, 88.5, 125.8, 127.4, 127.6, 127.7, 127.9, 128.2, 129.3, 131.6, 133.0, 135.2, 135.3, 136.1, 139.0, 143.8, 164.6, 171.5; HRMS (ESI): Calcd for $C_{28}H_{28}ClNNaO_7S$, $[M + Na]^+$: 580.1167; Found: 580.1142.

*(Z)-Dimethyl5-(benzyloxy)-2-(4-methylphenylsulfon-amido)-5-phenyl-4-p-tolylhex-2-enedioate(**5l**).* Amorphous powder, yield: 56%, dr: >95:5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 2.39 (s, 3H), 3.54 (s, 3H), 3.78 (s, 3H), 4.36 (d, J = 11.6 Hz, 1H), 4.60 (d, J = 12.0 Hz, 1H), 4.75 (d, J = 10.4 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 7.20 (m, 6H), 7.32 (m, 4H), 7.54 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 21.5, 52.1, 52.4, 52.9, 68.1, 88.6, 125.9, 127.0, 127.3, 127.4, 127.6, 128.1, 128.2, 128.3, 129.2, 130.2, 133.2, 135.4, 136.7, 136.9, 138.3, 139.1, 143.5, 164.7, 171.4; HRMS

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(ESI): Calcd for $C_{35}H_{35}NNaO_7S$, $[M + Na]^+$: 636.2026; Found: 636.2031.

*(Z)-Dimethyl 5-(benzyloxy)-4-(4-bromophenyl)-2-(4-methylphenylsulfonamido)-5- phenylhex-2-enedioate (**5m**).* Colorless solid, mp: 128−129 °C, yield: 68%, dr: >95:5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 3H), 3.42 (s, 3H), 3.69 (s, 3H), 4.26 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 12.4 Hz, 1H), 4.78 (d, J = 10.8 Hz, 1H), 6.16 (s, 1H), 6.79 (d, J = 8.0 Hz, 2H), 7.06−7.14 (m, 10H), 7.17−7.28 (m, 5H), 7.39 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 52.2, 52.5, 52.9, 68.2, 88.3, 121.4, 125.8, 127.0, 127.4, 127.8, 127.9, 128.3, 128.4, 129.3, 130.6, 132.1, 135.5, 135.7, 136.1, 138.2, 138.9, 143.7, 164.5, 171.4; HRMS (ESI): Calcd for $C_{34}H_{32}BrNNaO_7S$, $[M + Na]^+$: 700.0975; Found: 700.1010.

*(Z)-Dimethyl 5-(benzyloxy)-4-(3-bromophenyl)-2-(4-methylphenylsulfonamido)-5- phenylhex-2-enedioate (**5n**).* Amorphous powder, yield: 63%, dr: >95:5; ^{1}H NMR(400 MHz, $CDCl_3$): δ 2.27 (s, 3H), 3.42 (s, 3H), 3.66 (s, 3H), 4.25 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 11.6 Hz, 1H), 4.72 (d, J = 10.8 Hz, 1H), 6.26 (s, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.90 (t, J = 10.8, 8.0 Hz, 1H), 7.05−7.15 (m, 9H), 7.16−7.27 (m, 5H), 7.39 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 52.3, 52.6, 53.2, 68.2, 88.4, 121.4, 126.2, 126.9, 127.4, 127.4, 127.8, 127.9, 128.4, 128.4, 128.9, 129.3, 130.3, 133.2, 135.4, 136.2, 138.3, 138.4, 139.0, 143.8, 164.6, 171.3; HRMS (ESI): Calcd for $C_{34}H_{32}BrNNaO_7S$, $[M + Na]^+$: 700.0975; Found: 700.0995.

*(Z)-Dimethyl 5-(benzyloxy)-4-(4-fluorophenyl)-2-(4-methylphenylsulfonamido)-5- phenylhex-2-enedioate (**5o**).* Amorphous powder, yield: 78%, dr: >95:5; ^{1}H NMR(400 MHz, $CDCl_3$): δ 2.28 (s, 3H), 3.43 (d, J = 5.2 Hz, 3H), 3.67 (s, 3H), 4.27 (d, J = 12.0 Hz, 1H), 4.54 (dd, J = 11.6, 11.2 Hz, 1H), 4.75 (dd, J = 10.8,10.8 Hz, 1H), 6.22 (d, J = 25.6 Hz, 1H), 6.74 (m, 1H), 6.86 (m, 2H), 7.13−7.19 (m,11H), 7.24−7.28 (m, 5H), 7.41(dd, J = 8.0, 8.8 Hz, 2H); ^{13}C NMR(100 MHz, $CDCl_3$): δ 21.5, 52.2, 52.2, 52.4, 52.5, 52.6, 53.4, 68.2, 68.2, 88.5, 88.6, 114.2, 114.4, 125.7, 125.9, 127.0, 127.3, 127.3, 127.4, 127.4, 127.5, 127.7, 127.8, 127.8, 128.0, 128.2, 128.3, 129.2, 130.4, 131.9, 132.0, 135.5, 136.2, 136.4, 136.5, 138.3, 138.3, 139.0, 139.0, 143.5, 143.7, 164.6, 164.7, 171.5; HRMS (ESI): Calcd for $C_{34}H_{32}NFNaO_7S$, $[M + Na]^+$: 640.1776; Found: 640.1750.

*(Z)-Dimethyl 5-(benzyloxy)-2-(4-methylphenylsulfon-amido)-4,5-diphenylhex-2- ene-dioate (**5p**).* Amorphous powder, yield: 57%, dr: >95:5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.27 (s, 3H), 3.43 (s, 3H), 3.67 (s, 3H), 4.26 (d, J = 12.0 Hz, 1H), 4.52 (d, J = 11.6 Hz, 1H), 4.71 (d, J = 10.4 Hz, 1H), 6.29 (s, 1H), 6.85 (d, J = 7.6 Hz, 2H), 7.04−7.10 (m, 10H), 7.12−7.27 (m, 8H), 7.41 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 52.2, 52.5, 53.4, 68.2, 88.6, 125.9, 127.0, 127.3, 127.4, 127.4, 127.5, 127.7, 128.0, 128.2, 128.3, 129.3, 130.4, 135.5, 136.4, 136.5, 138.3, 139.0, 143.5, 164.7, 171.5; HRMS (ESI): Calcd for $C_{34}H_{33}NNaO_7S$, $[M + Na]^+$: 622.1870; Found: 622.1837.

*(Z)-Dimethyl5-(benzyloxy)-2-(4-methylphenylsulfon-amido)-4-(4-nitrophenyl)-5-phenylhex-2-enedioate (**5q**).* Amorphous powder, yield: 64%, dr: >95:5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H), 3.46 (s, 3H), 3.77 (s, 3H), 4.35 (d, J = 12.4 Hz, 2H), 4.68 (d, J = 11.6 Hz, 2H), 5.13 (d, J = 10.8 Hz, 2H), 6.16 (s, 1H), 7.15 (d, J = 7.5 Hz, 2H), 7.23−7.32 (m, 13H), 7.34−7.44 (m, 6H), 7.99 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 164.2, 146.9, 144.8, 144.0, 138.6, 138.1, 135.8, 135.5, 131.4, 129.8, 129.5, 129.3, 128.6, 128.5, 128.4, 128.1, 127.5, 127.4, 127.2, 127.0, 126.1, 122.4, 88.2, 68.4, 53.4, 52.6, 52.4, 21.5; HRMS (ESI): Calcd for $C_{34}H_{32}N_2NaO_9S$, $[M + Na]^+$: 667.1721; Found: 667.1744.

*(Z)-Dimethyl-2-((4-methylphenyl)sulfonamido)-4,5-diphenyl-5-(2-(trimethylsilyl)ethoxy)hex-2- enedioate (**5r**).* Amorphous powder, yield: 70%, dr: >95:5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 7.9 Hz, 2H), 7.27−7.09 (m, 7H), 7.09−6.99 (m, 5H), 6.76 (d, J = 3.8 Hz, 3H), 4.50 (d, J = 10.4 Hz, 1H), 3.73 (s, 3H), 3.55 (s, 3H), 3.53−3.42 (m, 1H), 3.36 (td, J = 10.3, 5.5 Hz, 1H), 2.34 (s, 3H), 1.15−1.02 (m, 1H), 1.02−0.89 (m, 1H), −0.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 166.3, 145.0, 139.9, 138.1, 137.6, 136.8, 131.6, 130.8, 129.4, 129.3, 128.9, 128.8, 128.6, 127.7, 89.9, 78.8, 78.7, 78.5, 78.2, 65.2, 54.5, 53.9, 53.5, 22.9, 20.2; HRMS (ESI): Calcd for $C_{32}H_{39}NO_7SSiNa$, $[M + Na]^+$: 632.2124; Found: 632.2113.

The procedure for preparation of 6p from 5p. 5p. (120 mg, 0.2 mmol) was hydrogenated using H_2 (1 atm) and 10% Pd/C (10% equivalents) at room temperature overnight. The catalyst was filtered and washed with methanol twice. The combined washings and filtrate were evaporated *in vacuo* to give the crude product. A portion of crude product was subjected to ^{1}H NMR analysis for determination of diastereoselectivity. The crude product was purified by column chromatography on silica gel (eluent: ethyl acetate/petroleum ether =1:3) to afford the corresponding product **6** (94 mg, 92%) as colorless solid.

*Dimethyl 2-hydroxy-5-(4-methylphenylsulfonamido)-2,3-diphenylhexane-dioate(**6p**).* Colorless solid, mp: 102−103 °C, yield: 90%, dr: 93:7; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.3 Hz, 2H), 7.41−7.34 (m, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.19−7.07 (m, 3H), 7.04 (t, J = 2.4 Hz, 5H), 5.08 (d, J = 8.5 Hz, 1H), 3.92 (s, 3H), 3.84 (dd, J = 11.3, 1.8 Hz, 1H), 3.76−3.70 (m, 1H), 3.54 (s, 1H), 3.40 (s, 3H), 2.40 (s, 3H), 1.65 (ddd, J = 14.1, 11.1, 2.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.1, 171.4, 142.6, 138.9, 135.7, 135.4, 129.2, 128.5, 126.7, 126.6, 126.4, 126.3, 125.8, 124.5, 80.8, 53.1, 52.7, 51.4, 48.3, 35.1, 20.5; HRMS (ESI): Calcd for $C_{27}H_{29}NO_7SNa$, $[M + Na]^+$: 534.1562; Found: 534.1566.

The procedure for preparation of 7p from 5p. To a solution of **5p** (60.7 mg, 0.10 mmol), $CuCl_2$ (17.0 mg, 0.10 mmol) and DDQ (45.4 mg, 0.20 mmol) in 5 mL DCM, The resulting mixture was stirred at room temperature for 3 days. TLC indicated the reaction was complete. The crude products were filtered through Cleanert Alumina (N) and concentrated. A portion of crude product was subjected to ^{1}H NMR analysis for determination of diastereoselectivity. The residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether =1:3) to afford **7p** as colorless powder (37.5 mg, 72%).

The procedure for preparation of 7p from 5r. To a solution of **5r** (170.5 mg, 0.28 mmol) in 5 mL DCM, $BF_3{\cdot}OEt_2$ (200 μL, 227 mg, 1.60 mmol) was introduced via a syringe. The resulting mixture was stirred at room temperature for 2 h, and the reaction was quenched with a solution of saturated $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. A portion of crude product was subjected to ^{1}H NMR analysis for determination of diastereoselectivity. The residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether =1:3) to afford **7p** as colorless powder (128.3 mg, 90%).

*(Z)-Dimethyl5-hydroxy-2-((4-methylphenyl)sulfonamido)-4,5-diphenylhex-2-enedioate(**7p**).* Amorphous powder, yield: 90%, dr: >95:5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.52 (d, J = 7.7 Hz, 3H), 7.44 (d, J = 7.3 Hz, 2H), 7.29 (d, J = 10.6 Hz, 2H), 7.17 (dd, J = 11.9, 6.4 Hz, 6H), 7.06 (s, 6H), 6.47 (m, 1H), 4.98 (d, J = 10.6 Hz, 1H), 3.83 (s, 3H), 3.54 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 165.0, 144.0, 139.5, 138.8, 136.2, 135.9, 130.1, 129.4, 127.9, 127.8, 127.6, 127.5, 127.0, 126.0, 125.5, 81.1, 53.8, 52.8, 51.2, 21.5; HRMS (ESI): Calcd for $C_{27}H_{27}NO_7SNa$, $[M + Na]^+$: 532.1407; Found: 532.1414.

The procedure for preparation of 8p from 7p. A mixture of compound **7p** (104.8 mg, 0.20 mmol), *p*-toluenesulfonic acid (TsOH H_2O) (112.0 mg, 0.60 mmol) and toluene (6 mL) was refluxed for 5 h. TLC indicated the reaction was complete. The reaction mixture was cooled to room temperature. The solvent was removed under vacuum to give the crude product. A portion of crude product was subjected to ^{1}H NMR analysis for determination of diastereoselectivity.The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether =1:10) to give the product **8p** (56.6 mg, 85% yield) as yellow oil.

*Dimethyl 3-(4-nitrophenyl)-2-phenyl-2,3-dihydrofuran-2,5-dicarboxylate (**8p**).* Yellow oil, yield: 85%, dr: >95:5; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, J = 6.6 Hz, 2H), 7.06−6.89 (m, 6H), 6.85 (d, J = 6.2 Hz, 2H), 6.09 (s, 1H), 5.05 (s, 1H), 3.84 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 160.2, 147.1, 136.5, 134.7, 129.2, 127.9, 127.6, 127.3, 125.8, 116.0, 94.4, 56.5, 53.4, 52.4; HRMS (ESI): Calcd for $C_{20}H_{18}O_5Na$, $[M + Na]^+$: 361.1052; Found: 361.1047.

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■ ASSOCIATED CONTENT

Supporting Information

Text, figures, and CIF files giving NMR spectra of new compounds and X-ray diffraction analysis data for *Z-anti*-**5g**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: syliu@sist.ecnu.edu.cn.

*E-mail: whu@chem.ecnu.edu.cn.

Notes

The authors declare no competing financial interest.

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