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Enantioselective Synthesis of Hydantoin and Diketopiperazine-Fused Tetrahydroisoquinolines via Pictet−Spengler Reaction

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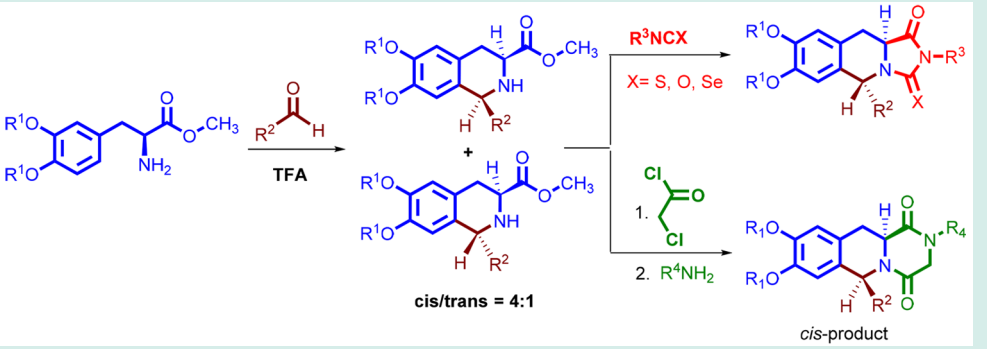
Supporting Information



ABSTRACT: An enantioselective synthesis of iso-, isothio-, and isoselenohydantoin and diketopiperazine-fused tetrahydroisoquinolines from L-Dopa was reported. The route consists of an Pictet−Spengler reaction of (*S*)-2-amino-3-(3,4-dimethoxyphenyl)propanoates with various aldehydes to afford diastereomeric tetrahydroisoquinolines. Next step, the tetrahydroisoquinolines were further reacted with iso-, isothio-, or isoselenocyanates to construct hydantoin. Similarly, the diketopiperazine moiety was constructed by subjecting tetrahydroisoquinolines to a condensation reaction with chloroacetyl chloride followed by nucleophilic addition with various primary amines.

KEYWORDS: *enantioselective synthesis, diketopiperazine-fused tetrahydroisoquinolines, hydantoin-fused tetrahydroisoquinolines, molecular hybridization, Pictet−Spengler reaction*

INTRODUCTION

Hydantoin is a privileged scaffold found in various natural products and bioactive compounds.[1] Notably, indoline thiohydantoin acts as an antiproliferative agent against prostate tumor,[2] benzylidene-thiohydantoin shows potent tyrosinase inhibition,[3] and enzalutamide is used for the treatment of castration-resistant prostate cancer.[4] From many years, selenium-containing compounds are restrained to utilize in the medicines due to their presumed toxic nature until the discovery of L-selenomethionine, methylselenocysteine, and various selenoproteins which are beneficial to human health.[5] Some selenoorganic compounds exhibit promising bioactivities. For example, Ebselen acts as an antioxidant, whereas 2-selenohydantoin displays good anticancer activity.[6,7]

Among various heterocycles, in particular, the tetrahydroisoquinoline motif is an integral part of numerous natural products and bioactive compounds. For example, dihydroisoquinoline carbothioamide is an agonist for capsaicin receptor[8] and almorexant is a dual orexin receptor antagonist.[9,10]

2,5-Diketopiperazines are naturally occurring cyclic dipeptides found in marine organisms, fungi and bacteria. Their structural simplicity, conformationally constrained scaffold, and ability to mimic peptide properties make them a useful pharmacophore in drug discovery.[11] For example, cyclo[Dmt-Tic] is an opioid antagonist showing a good δ-selective binding affinity (Figure 1).[12]

Assembling two or more dissimilar privileged scaffolds in a single framework to yield hybrid molecules is an interesting strategy in drug discovery.[13] This method has successfully provided potent anticonvulsant,[14] antimycobacterial,[15] bone anabolic,[16] tankyrase inhibitor,[17] antitumor,[18,19] and antitubercular[20] agents (Figure 2).

An exhaustive literature survey revealed several methods for the synthesis of tetrahydro-β-carboline-fused (thio)-hydantoins.[21] However, tetrahydroisoquinoline-embedded thio(seleno)hydantoin and tetrahydroisoquinoline-fused diketopiperazine are less explored (Figure 3). Prompted by the scarcity of the related reports and as a part of our continuing effort toward the synthesis of fused heterocycles,[22] we report herein an enantioselective of hydantoin-fused tetrahydroiso-

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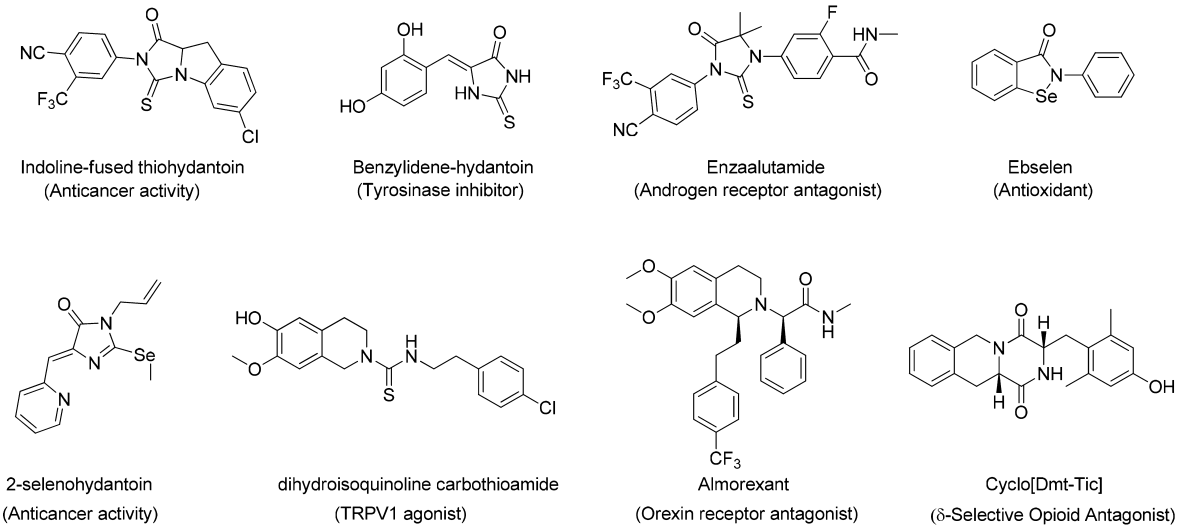

Figure 1. Bioactive hydantoins, tetrahydroisoquinolines, and 2,5-diketopiperazines.

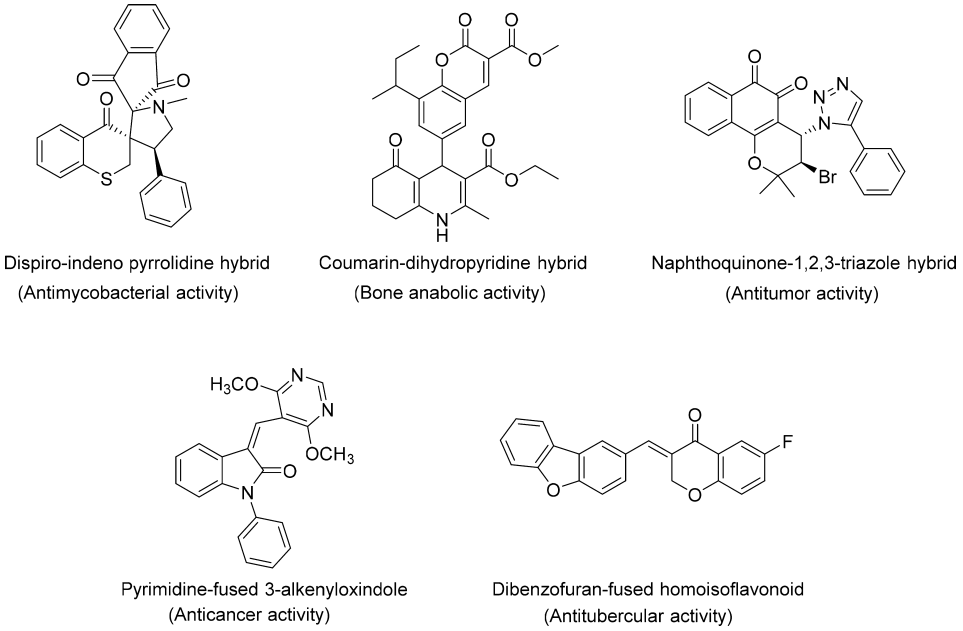

Figure 2. Biologically potent hybrid molecules.

quinolines **9** and diketopiperazine-fused tetrahydroisoquinolines **12** via Pictet–Spengler condensation of (*S*)-2-amino-3-(3,4-dimethoxyphenyl)propanoates **5** with aldehydes. The tetrahydroquinolines **7** thus obtained were reacted either with isocyanates or chloroacetyl chloride and amines.

RESULTS AND DISCUSSION

The synthesis of methyl (*S*)-2-amino-3-(3,4-dimethoxyphenyl)propanoate **5**{*1*} was started with the esterification of L-Dopa in the presence of thionyl chloride and methanol to yield ester **2** in a good yield. Boc protection, followed by alkylation afforded compound **4**{*1*} in 88% yield. Finally, TFA-mediated deprotection of the Boc group yielded methyl ester amine **5**{*1*} in 98% yield (Scheme 1). The optical purity of **5**{*1*} was confirmed by chiral HPLC (see SI, page S17).

The reaction between **5**{*1*} and 4-nitrobenzaldehyde **6**{*1*} was chosen as a model reaction to examine various reaction conditions. Accordingly, treatment of **5**{*1*} with 4-nitrobenzaldehyde **6**{*1*} in the presence of K_2CO_3 in methanol did not afford any product and the starting materials were recovered (Table 1, entry 1). The use of strong base KO^{t}Bu or organic bases like triethyl amine or piperidine yielded only imine. (Table 1, entries 2–4). The refluxing of a mixture of **5**{*1*} and 4-nitrobenzaldehyde **6**{*1*} in the presence of catalytic amount of *p*-TSA in acetonitrile gave **7**{*1,1*} as a diastereomeric mixture in only 20% yield because of electron deficient nature of tertahydroquinoline ring compared to tryptophan moiety (Table 1, entry 5). The diastereomers **7**{*1,1*}-*cis* and **7**{*1,1*}-*trans* were separated by column chromatography in 4:1 ratio and the relative stereochemistry of the compounds was assigned on the basis of NOE study and crystallographic analysis. Accordingly, when C_3–H proton of **7**{*1,1*}-*cis* was irradiated, enhancement of the signal of C_1–H was observed indicating corresponding protons were on the same side of the tertahydroquinoline ring, whereas C_3–H and

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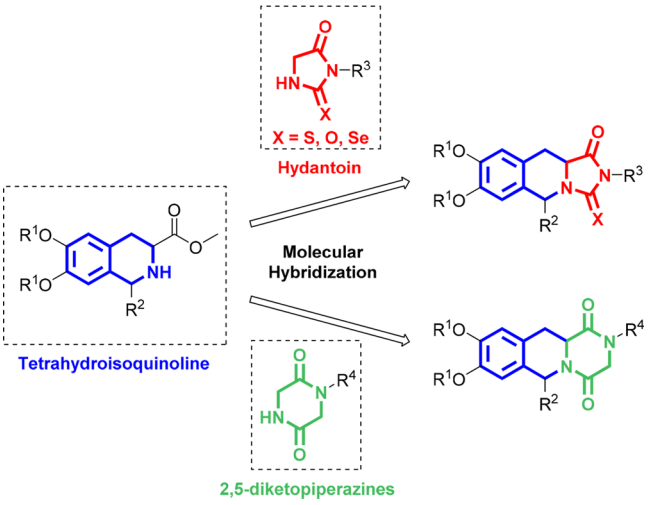

Figure 3. Molecular hybridization of tetrahydroisoquinoline with hydantoin and 2,5-diketopiperazine.

C-$_1$H of 7{*1,1*}-*trans* did not show any correlation (S34−S35). ORTEP diagram of 7{*1,1*}-*cis* and 7{*1,1*}-*trans* showed that the tertahydroquinoline ring adopted half-chair conformation. The bulky methyl ester and 4-nitrophenyl groups oriented themselves in a pseudo equatorial position, whereas C_1−H and C_3−H hydrogens acquired axial position and oriented in a *cis* and *trans* way, respectively. (Figure 4).

The screening of various Lewis acids, such as $TiCl_4$, $AlCl_3$, and $BF_3{\cdot}Et_2O$, afforded expected products in poor to moderate yields (Table 1, entries 6−8). When 20 mol % of TFA was used, the product was obtained in only 52% yield after 48 h reflux (Table 1, entry 9). The use of toluene as a solvent diminished the yield of the products (Table 1, entry 10). When the same reaction was carried out in refluxing chloroform in 20 mol % TFA the yield was 70% albeit, in longer reaction time (Table 1, entry 11). Finally, when **5**{*1*} and nitrobenzaldehyde **6**{*1*} were treated with two equivalents of TFA in refluxing chloroform for 24 h, the desired products were obtained in an excellent yield (Table 1, entry 12).

With the diastereomeric compound 7{*1,1*} in hand, we then carried out the construction of hydantoin moiety through one-pot urea formation followed by intramolecular cyclization (Scheme 2).

Consequently, the diastereomeric mixture was treated with methyl isothiocyanate in the presence of K_2CO_3 in dichloromethane at room temperature and only a new spot was observed on TLC. Chromatographic isolation and the ^{1}H NMR analysis indicated the formation of a single *trans*-isomer. To our surprise, further analysis of the new product by a chiral HPLC revealed two peaks on the chromatogram (see SI, page 36).

Subsequently, we decided to investigate the current reaction by treating both the diastereomers 7{*1,1*}-*cis* and 7{*1,1*}-*trans*, separately. Accordingly, the treatment of 7{*1,1*}-*cis* with methyl isothiocyanate yielded **9**{*1,1,1*}-*epimer* (*trans*) as the only product. The complete conversion of 7{*1,1*}-*cis* to **9**{*1,1,1*}-*epimer* (*trans*) was observed because of the epimerization of the chiral center adjacent to the carbonyl carbon to yield the thermodynamically more stable trans isomer.

Conversely, the 7{*1,1*}-*trans* afforded **9**{*1,1,1*}-*trans* exclusively under similar condition (Scheme 2). A representative example of the isomer **9**{*2,7,2*} was confirmed by X-ray crystal structure analysis (Figure 5).

With the optimized condition in hand, we then examined the substrate scope by reaction of substituted **7**-*trans* with a variety of iso-, isothiocyanates, and isoselenocyanates. The required isoselonocyanates were prepared from selenium powder and in situ generated isocyanide from *N*-formyl amines and triphosgene.[23] All the corresponding products were obtained in good to excellent yield; and no racemization was observed in each case (Table 2).

The scope of this strategy was further extended for the synthesis of fused pyrazino tetrahydroisoquinolines **12**. Accordingly, when a mixture of 7{*1,1*}-*cis* and 7{*1,1*}-*trans* was treated with chloroacetyl chloride under basic condition followed by double nucleophilic addition reaction with amine **11**{*1*}, surprisingly, no epimerization was observed and the reaction yielded corresponding **12**{*1,1,1*}-*cis* and **12**{*1,1,1*}-*trans* in 4:1 diastereomeric ratio after column separation (Scheme 3) (S37).

The conformational analysis of compounds **12**{*1,1,1*}-*cis* and **12**{*1,1,1*}-*trans* were made based on NOESY experiment. Proton attached to C3 carbon displayed characteristic through-space interaction with proton attached to C1 carbon for the compound **12**{*1,1,1*}-*cis*, whereas these interactions were absent in the case of **12**{*1,1,1*}-*trans* (S38−S39). A single crystal X-ray analysis of **12**{*1,1,4*} exhibited that the bicyclic fused-ring framework existed in *cis*-decalin-like conformation (Figure 6).

Subsequently, substrate scope of the reaction for the synthesis of pyrazino tetrahydroisoquinolines **12** from acyl chloride[24] and various amines was investigated (Table 3). All the desired products were obtained in an excellent yield with high diastereoselectivity.

Scheme 1. Synthesis of Methyl (*S*)-2-Amino-3-(3,4-dimethoxyphenyl)propanoate 5{*1*}

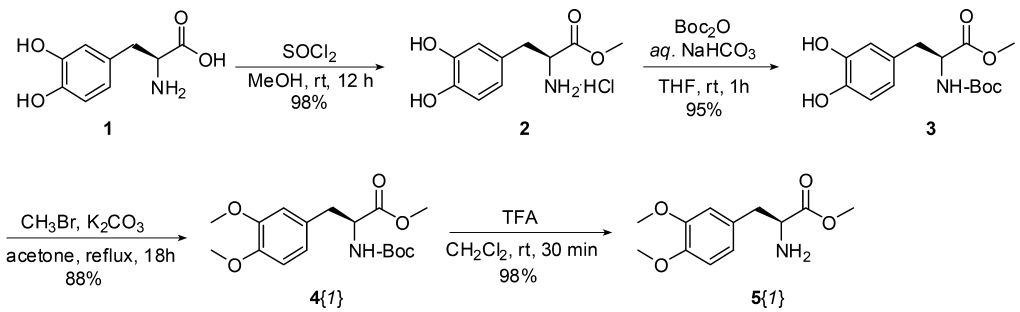

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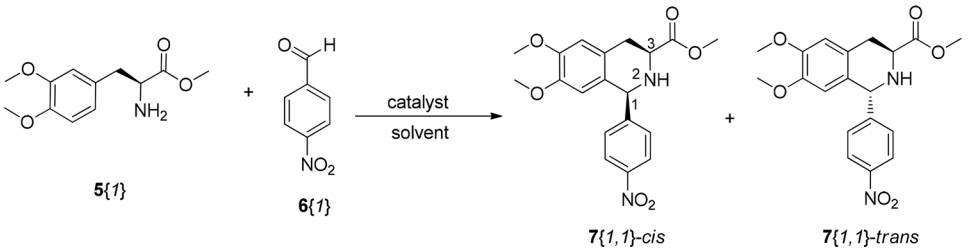
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (mol %)	base (equiv)	solvent	time (h)	7{1,1}-*cis*/7{1,1}-*trans*	yield (%)
1		K_2CO_3 (1.5)	MeOH	24		N.R.
2		KO*t*Bu (1.5)	CH_3CN	24		0[b]
3		Et_3N (1.5)	CH_3CN	24		0
4	piperidine (20)		CH_3CN	24		0
5	*p*-TSA (20)		CH_3CN	24	4:1	20
6	$TiCl_4$ (20)		CH_3CN	24	4:1	69
7	$AlCl_3$ (20)		CH_3CN	48	4:1	62
8	$BF_3{\cdot}Et_2O$ (20)		CH_3CN	24	4:1	27
9	TFA (20)		CH_3CN	48	4:1	52
10	TFA (20)		toluene	36	4:1	43
11	TFA (20)		$CHCl_3$	48	4:1	70
12	TFA (200)		$CHCl_3$	24	4:1	92

[a]Reaction conditions: 5{*1*} (0.41 mmol), 4-nitrobenzaldehyde 6{*1*} (0.62 mmol), base (1.5 equiv), catalyst, $MgSO_4$ (0.41 mmol), solvent (10 mL), and reflux. [b]Imine formation

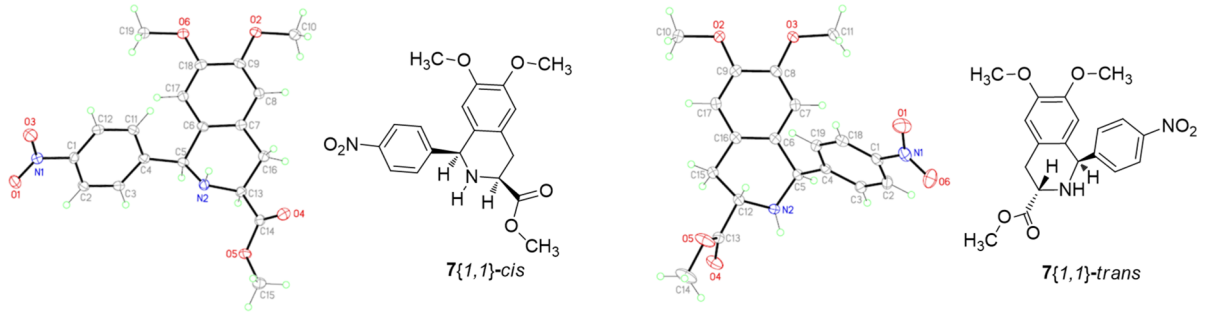
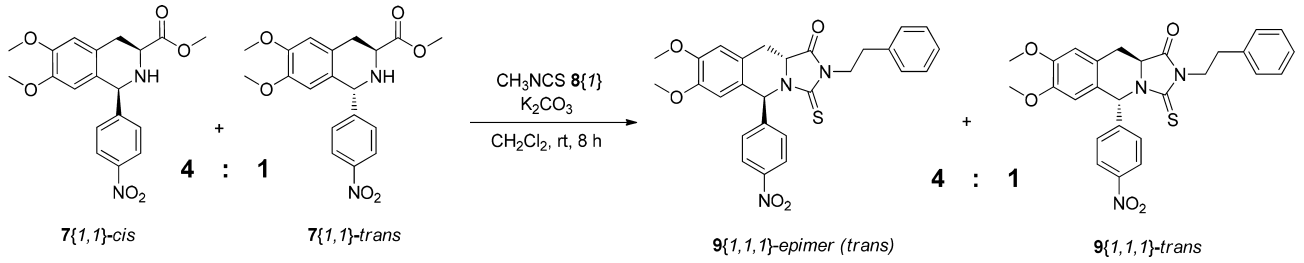


Figure 4. ORTEP diagrams of diastereomers 7{*1,1*}-*cis* and 7{*1,1*}-*trans*. (Atomic displacement ellipsoids are drawn at the 50% probability level.)

Scheme 2. Treatment of 7{*1,1*}-*cis* and 7{*1,1*}-*trans* with Methyl Isothiocyanate 8{*1*}



CONCLUSION

In conclusion, a straightforward synthesis of optically pure hydantoin-fused tetrahydroisoquinolines and diketopiperazine-fused tetrahydroisoquinolines has developed. Initially, (*S*)-2-amino-3-(3,4-dimethoxyphenyl)propanoates were obtained by a series of functional group transformations from L-Dopa and reacted with aldehydes via Pictet−Spengler reaction to deliver tetrahydroisoquinolines as a diastereomeric mixture in 4:1 (*cis*/trans) ratio. *trans*-Tetrahydroisoquinolines were readily reacted with iso-, isothio-, and isoselenocyanates, and the reaction proceeded through urea formation, followed by cyclization to afford hydantoin-embedded tetrahydroisoquinolines. Likewise, the synthesis of diketopiperazine-embedded tetrahydroisoquinolines employed condensation reaction of *cis*-tetrahydroisoquinolines with chloroacetyl chloride, followed by double nucleophilic addition with primary amines. A direct synthesis, enantioselectivity, and broad substrate scope are the key features of this method.

EXPERIMENTAL SECTION

General Methods. ^1H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra were recorded on 400-MR automated

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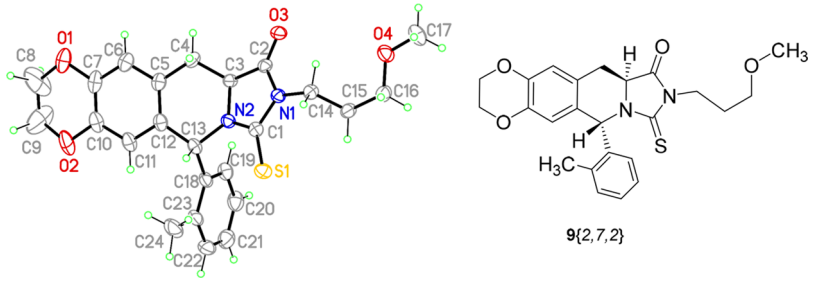

Figure 5. ORTEP diagram of imidazo[1,5-*b*]isoquinolin-10(6*H*)-one **9**{*2,7,2*}. (Atomic displacement ellipsoids are drawn at the 50% probability level.)

spectrometer. Chemical shifts are reported in parts per million (ppm) on the δ scale from an internal standard (TMS). Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel-coated Kiselgel 60 F_{254} plates. Flash chromatography was performed using the indicated solvent and silica gel 60 (Merck, 230−400 mesh). High-resolution mass spectra (HRMS) were recorded in ESI mode using TOF mass spectrometer. IR spectra were obtained using FT-IR spectrometer. Enantiomeric excess (*ee*) was determined by chiral HPLC equipped with a Lux 5 μ cellulose-1 (250 × 4.6 mm) analytical column. Melting point was recorded with Yanaco micromelting point apparatus and was uncorrected. All materials were purchased from commercial sources and used without further purification.

General Procedure for the Synthesis of Methyl (1*R*,3*S*)-Methyl 6,7-dimethoxy-1-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate 7{*1,1*}. To a stirred solution of methyl (*S*)-2-amino-3-(3,4-dimethoxyphenyl)propanoate **5**{*1*} (1 g, 4.17 mmol) in chloroform was added 4-nitrobenzaldehyde **6**{*1*} (0.947 g, 6.26 mmol) and trifluoroacetic acid (200 mmol) at room temperature and the reaction mixture was refluxed for 24 h. After completion of the reaction, the solvent was evaporated. The reaction mixture was neutralized with sat. $NaHCO_3$ solution (30 mL) and extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with brine solution (20 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography (15−20% ethyl acetate in hexanes) to afford (1*R*,3*S*)-methyl 6,7-dimethoxy-1-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate 7{*1,1*} (1.33 g, 86%).

7{1,1}-trans. Yellow solid (15%, 120 mg); mp 141−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 6.66 (s, 1H), 6.05 (s, 1H), 5.23 (s, 1H), 3.89 (m, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.59 (s, 3H), 3.06−3.16 (m, 2H), 2.30 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 151.2, 148.1, 147.6, 130.0, 128.3, 126.1, 123.8, 111.5, 110.0, 61.9, 56.0, 55.8, 52.3, 31.9; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{21}N_2O_6$ 373.1400, Found 373.1399; $[\alpha]^{27}_D$ = −94.44 (c = 0.034, CH_2Cl_2); HPLC analysis: column- Lux 5 μ cellulose-1 (250 × 4.6 mm), 15% *i*-PrOH/Hexane, 0.3 mL min^{-1}, 254 nm); 99% dr t_R = 12.1 min; IR (cm^{-1}, neat) 3338, 2999, 1517, 1347.

7{1,1}-cis. Yellow solid (77%, 120 mg); mp 126−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 6.66 (s, 1H), 6.25 (s, 1H), 5.34 (s, 1H), 3.88 (s, 3H), 3.76 (dd, J = 8.0 Hz, J = 3.0 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.17 (dd, J = 16.0 Hz, J = 3.0 Hz, 1H), 3.02 (dd, J = 20.0 Hz, J = 8.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 151.9, 148.2, 147.7, 147.2, 129.5, 126.6, 125.5, 123.6, 111.4, 110.4, 58.0, 55.8, 52.1, 51.8, 30.8; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{19}H_{21}N_2O_6$ 373.1400, Found 373.1399; $[\alpha]^{27}_D$ = +80.36 (c = 0.004, CH_2Cl_2); HPLC analysis column- Lux 5 μ cellulose-1 (250 × 4.6 mm), 15% *i*-PrOH/hexane, 0.3 mL min^{-1}, 254 nm); 99% dr t_R = 18.1 min; IR (cm^{-1}, neat) 3338, 2999, 1517, 1347.

Representative Procedure for the Synthesis of (5*R*,10*aS*)-7,8-Dimethoxy-5-(4-nitrophenyl)-2-phenethyl-3-thioxo-2,3,10,10*a*-tetrahydroimidazo[1,5-*b*]isoquinolin-1(5*H*)-one 9{*1,1,1*}. To the stirred solution of methyl (1*R*,3*S*)-6,7-dimethoxy-1-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate 7{*1,1*}-*trans* (200 mg, 0.537 mmol) in dichloromethane (10 mL) was added K_2CO_3 (0.22 mg, 1.611 mmol) and phenethyl isothiocyanate (96 mg, 0.590 mmol) and the reaction mixture was stirred at room temperature for 8 h. After completion of the reaction, reaction mixture was filtered and the crude product was purified by flash column chromatography (20−22% ethyl acetate in hexanes) to afford (5*R*,10a*S*)-7,8-dimethoxy-5-(4-nitrophenyl)-2-phenethyl-3-thioxo-2,3,10,10a-tetrahydroimidazo[1,5-*b*]-isoquinolin-1(5*H*)-one **9**{*1,1,1*}.

Yellow solid, (91%, 191 mg); mp 154−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.06−7.16 (m, 5H), 6.88 (s, 1H), 6.68 (s, 1H), 6.38 (s, 1H), 4.19 (dd, J = 11.2 Hz, J = 5.2 Hz, 1H), 3.96−4.03 (m, 2H), 3.81 (s, 3H), 3.63 (s, 3H), 3.19 (dd, J = 16.0 Hz, J = 5.2 Hz, 1H), 2.84−2.98 (m, 2H), 2.92 (dd, J = 12.0 Hz, J = 3.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.0, 172.7, 149.0, 148.7, 147.7, 147.6, 137.7, 129.9, 129.0, 128.4, 126.6, 124.3, 123.9, 123.2, 111.3, 110.5, 56.9, 56.0, 56.0, 54.5, 42.4, 33.4, 30.0; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{28}H_{26}N_3O_5S$ 504.1553, Found 504.1587; $[\alpha]^{27}_D$ = −522.69 (c = 0.82, CH_2Cl_2); HPLC analysis: column- Lux 5 μ cellulose-1 (250 × 4.6 mm), 15% *i*-PrOH/Hexane, 0.8 mL min^{-1}, 254 nm); 99% *ee* t_R = 50.4 min; IR (cm^{-1}, neat) 3002, 2853, 1748, 1348.

General Procedure for the Synthesis of (6*S*,11*aS*)-8,9-dimethoxy-6-(4-nitrophenyl)-2-propyl-2,3,11,11a-tetrahydro-4*H*-pyrazino[1,2-*b*]isoquinoline-1,4(6*H*)-dione 12{*1,1,1*}. A solution of methyl (1*S*,3*S*)-6,7-dimethoxy-1-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate 7{1,1}-*cis* (0.1 g, 0.268 mmol) and triethylamine (0.029 g, 0.295 mmol) in dichloromethane (15 mL) was cooled at 0 °C. To the above reaction mixture was added chloroacetyl chloride (0.088 g, 0.295 mmol) in a dropwise manner and the reaction mixture was stirred at room temperature for 1 h. After completion of the reaction, reaction mixture was diluted with *sat.* $NaHCO_3$ solution (20 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with brine solution (15 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash

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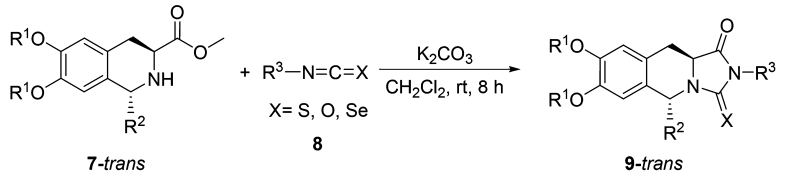
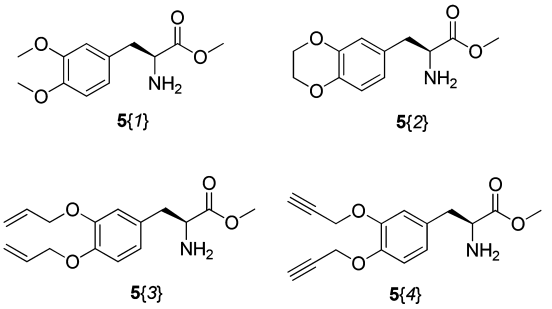
Table 2. Substrate Scope for the Synthesis of Imidazo[1,5-*b*]isoquinolinones 9[a]



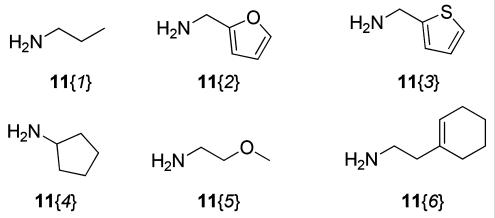
7-*trans* **9**-*trans*

α-Amino acid esters



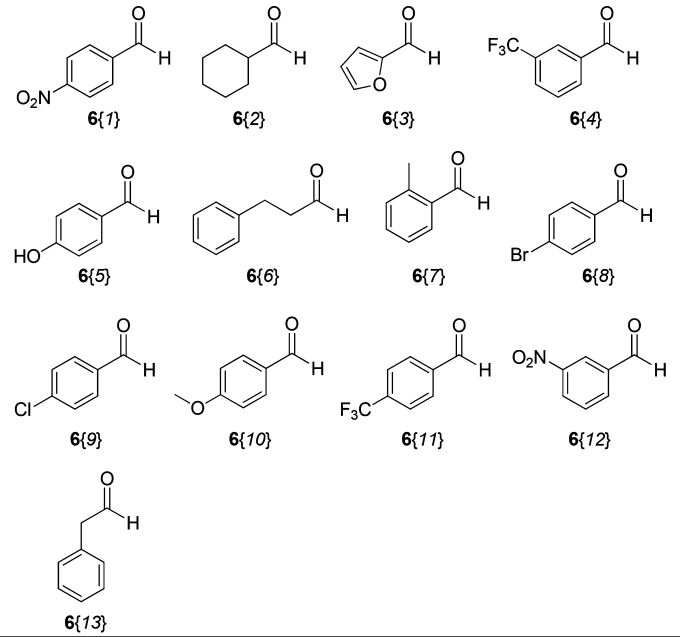
5{*1*} **5**{*2*} **5**{*3*} **5**{*4*}

Amines



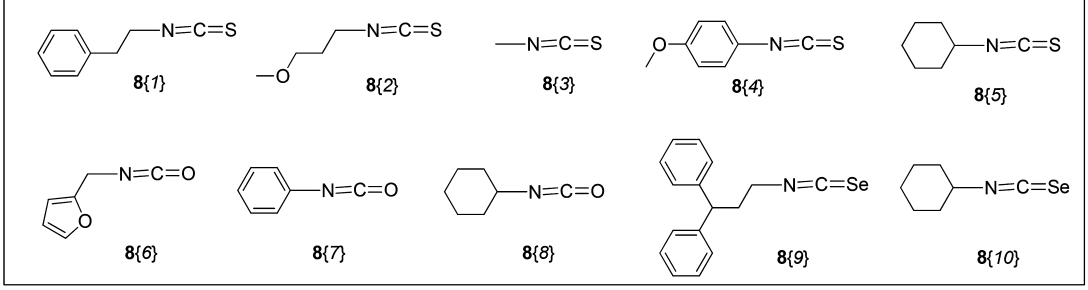
11{*1*} **11**{*2*} **11**{*3*} **11**{*4*} **11**{*5*} **11**{*6*}

Aldehydes

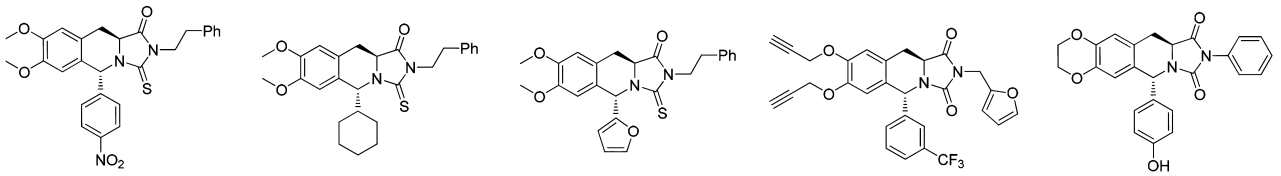


6{*1*} **6**{*2*} **6**{*3*} **6**{*4*} **6**{*5*} **6**{*6*} **6**{*7*} **6**{*8*} **6**{*9*} **6**{*10*} **6**{*11*} **6**{*12*} **6**{*13*}

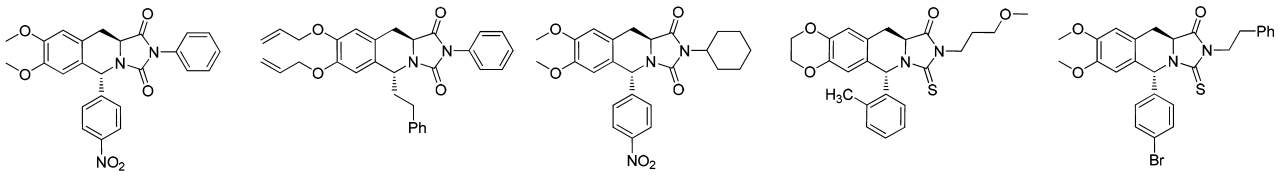
cyanates



8{*1*} **8**{*2*} **8**{*3*} **8**{*4*} **8**{*5*} **8**{*6*} **8**{*7*} **8**{*8*} **8**{*9*} **8**{*10*}



9{*1,1,1*}, 91%, 99% ee **9**{*1,2,1*}, 75%, 99% ee **9**{*1,3,1*}, 70%, 99% ee **9**{*4,4,6*}, 72%, 99% ee[b] **9**{*2,5,7*}, 70%, 99% ee[b]



9{*1,1,7*}, 78%, 99% ee[b] **9**{*3,6,7*}, 82%, 99% ee[b] **9**{*1,1,8*}, 72%, 99% ee[b] **9**{*2,7,2*}, 82%, 99% ee **9**{*1,8,1*}, 88%, 99% ee

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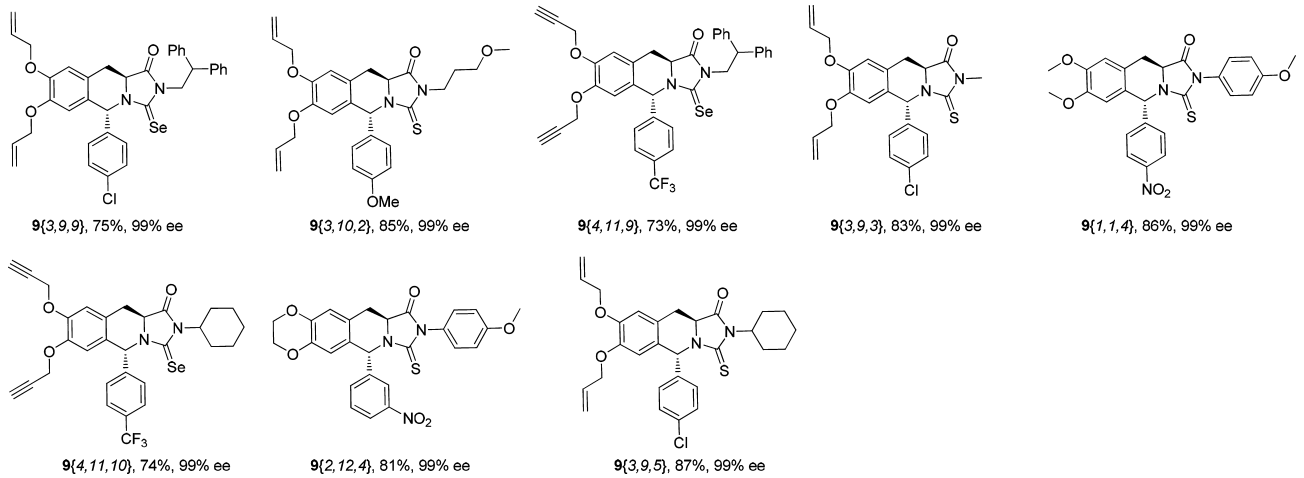
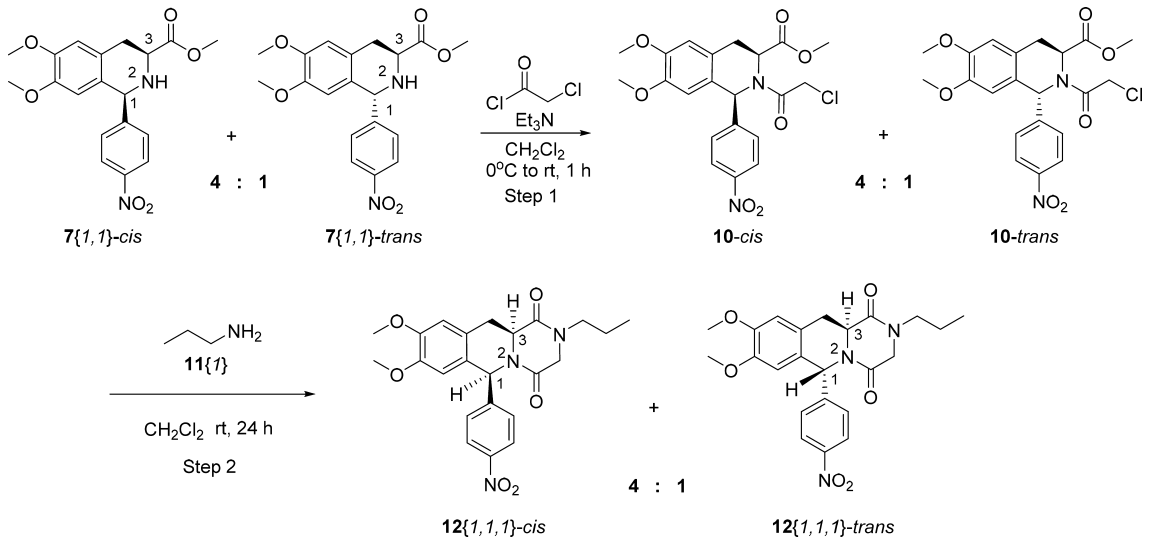
Table 2. continued



[a]Reaction conditions: 7-*trans* (0.53 mmol), cyanate **8** (0.59 mmol), K_2CO_3 (3 equiv), CH_2Cl_2 (10 mL). [b]NaH (3 equiv) was used.

Scheme 3. Treatment of a Mixture of 7{*1,1*}-*cis* and 7{*1,1*}-*trans* with Acyl Chloride and Amine 11{*1*}



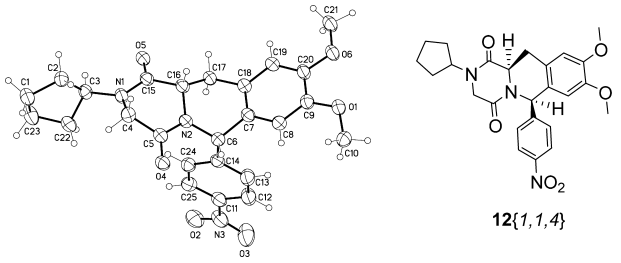


Figure 6. ORTEP diagram of pyrazino tetrahydroisoquinoline **12**{*1,1,4*}. (Atomic displacement ellipsoids are drawn at the 50% probability level.)

column chromatography (15−20% ethyl acetate in hexanes) to afford methyl (1*S*,3*S*)-2-(2-chloroacetyl)-6,7-dimethoxy-1-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **10**-*cis* (0.108 g, 90%). To the stirred solution of **10**-*cis* (0.108 g, 0.24 mmol) in dicholoromethane (15 mL) was added propyl amine **11**{*1*} (0.071 g, 1.2 mmol), and the reaction mixture was at room temperature for 24 h. After completion of the reaction, reaction mixture was diluted with water (15 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with brine solution (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (25−35% ethyl acetate in hexanes) to afford **12**{*1,1,1*}-*cis*.

Yellow solid, (97%, 178 mg); mp 132−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.9 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 6.81 (s, 1H), 6.79 (s, 1H), 6.45 (s, 1H), 4.12 (dd, J = 16.8, 1.0 Hz, 1H), 4.07 (dd, J = 12.6, 4.1 Hz, 1H), 3.94 (d, J = 16.8 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.54−3.46 (m, 1H), 3.38 (dt, J = 13.7, 7.2 Hz, 1H), 3.27 (dd, J = 15.8, 4.0 Hz, 1H), 2.89 (dd, J = 15.5, 12.5 Hz, 1H), 1.60 (hept, J = 7.4 Hz, 2H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 166.7, 149.1, 148.7, 148.6, 147.1, 127.4, 126.2, 126.2, 123.8, 111.5, 110.6, 57.6, 56.2, 56.1, 56.0, 50.7, 48.0, 29.8, 20.5, 11.1; HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{23}H_{26}N_3O_6$ 440.1816; Found 440.1816; $[\alpha]_D^{27}$ = −62.19 (c = 0.062, CH_2Cl_2); HPLC analysis column-Lux 5 μ cellulose-1 (250 × 4.6 mm), 66.7% *i*-PrOH/hexane, 0.8 mL min^{-1}, 254 nm); 99% *ee* t_R = 16.9 min; IR (cm^{-1}, neat) 3075, 2962, 1669, 1517.

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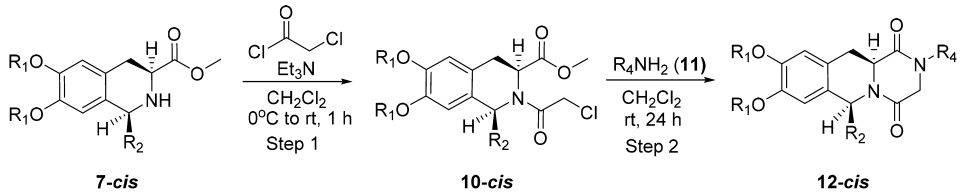
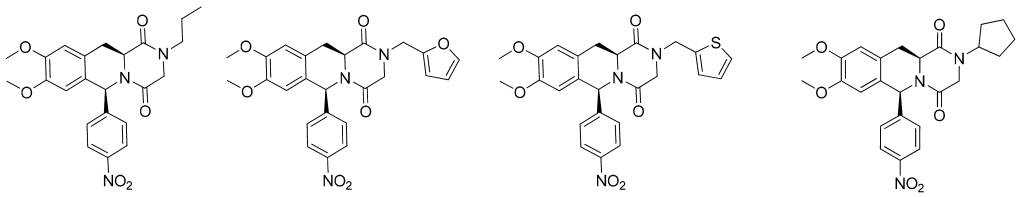
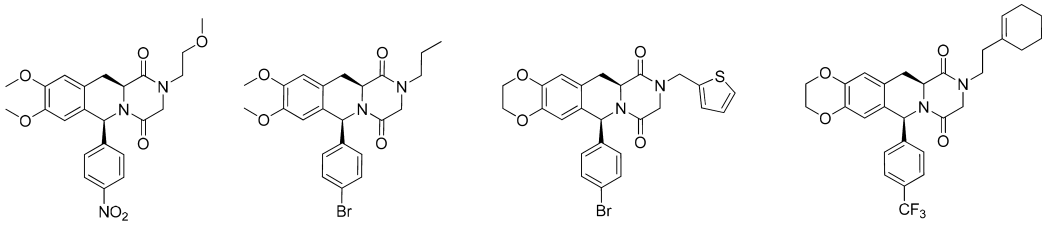
Table 3. Substrate Scope for the Synthesis of Pyrazino[1,2-*b*]isoquinolinones 11[a]



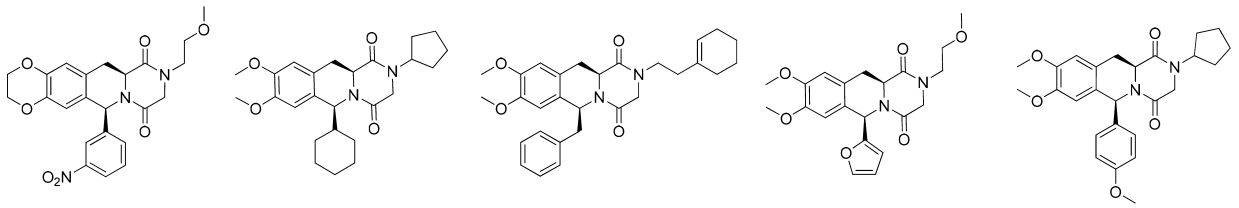
7-*cis* 10-*cis* 12-*cis*



12{1,1,1}, 97%, 99% ee 12{1,1,2}, 89%, 99% ee 12{1,1,3}, 85%, 99% ee 12{1,1,4}, 93%, 99% ee



12{1,1,5}, 96%, 99% ee 12{1,8,1}, 94%, 99% ee 12{2,8,3}, 82%, 99% ee 12{2,11,6}, 77%, 99% ee



12{2,12,5}, 90%, 99% ee 12{1,2,4}, 80 %, 99% ee 12{1,13,6}, 70%, 99% ee 12{1,3,5}, 72%, 99% ee 12{1,10,4}, 74%, 99% ee

[a]Reaction conditions: Step 1, 7-*cis* (0.26 mmol), triethyl amine (0.29 mmol), chloroacetyl chloride (0.29 mmol), CH_2Cl_2 (15 mL); Step 2, **10**-*cis* (0.24 mmol), amine **11** (1.2 mmol), CH_2Cl_2 (15 mL).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.9b00005.

Full spectroscopic data (^{1}H, ^{13}C NMR, HRMS, chiral HPLC, and IR) of compounds **9** and **12** (PDF)

X-ray crystallographic data of compound 7{*1,1*}-*cis* (CCDC 1888820) (CIF)

X-ray crystallographic data of compound 7{*1,1*}-*trans*(CCDC 1888816) (CIF)

X-ray crystallographic data of compound **9**{*2,7,2*} (CCDC 1888845) (CIF)

X-ray crystallographic data of compound **12**{*1,1,4*} (CCDC 1888846) (CIF)

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Notes

The authors declare no competing financial interest.

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(24) When the reaction was carried out using 3-chloropropionyl chloride, only O- and N-acryloylated product was obtained via dehydrochlorination.

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