JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

SmI_2-Mediated Intermolecular Coupling of γ-Lactam N-α-Radicals with Activated Alkenes: Asymmetric Synthesis of 11-Hydroxylated Analogues of the Lead Compounds CP-734432 and PF-04475270

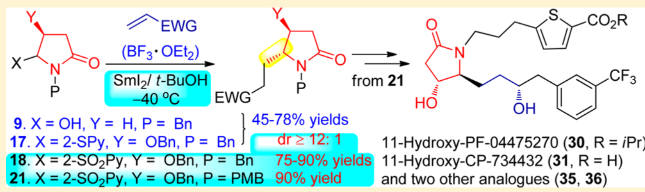
Kong-Zhen Hu,[†] Jie Ma,[‡] Shi Qiu,[†] Xiao Zheng,[†] and Pei-Qiang Huang*,[†]

[†]Department of Chemistry and Fujian Provincial Key Laboratory of Chemical Biology, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, PR China

[‡]Department of Pharmaceutical Chemistry, College of Pharmaceutical Sciences, Xiamen University, Xiamen, Fujian 361005, PR China

Supporting Information

ABSTRACT: We report, for the first time, the synthesis of 8-aza-analogues of PGE_2. The SmI_2-mediated cross coupling reactions of γ-lactam-hemiaminal **9**, lactam 2-pyridyl sulfide **17**, and lactam 2-pyridyl sulfone **18** with activated alkenes/alkyne were first developed, giving the corresponding γ-lactams in 49−78%, 45−75%, and 75−90%, respectively. The reactions of lactam 2-pyridyl sulfide and 2-pyridyl sulfone proceeded with ≥12:1 *trans*-diastereoselectivities. This represents the first intermolecular coupling reaction of the γ-lactam N-α-alkyl radicals of types **B**, **B1**, and **B2** with activated alkenes. Two radical-based mechanisms were suggested. The asymmetric synthesis of the 11-hydroxylated analogue of the highly selective EP_4 receptor agonist PF-04475270 (**30**), the 11-hydroxylated analogue of ocular hypotensive CP-734432 (**31**), compounds **35** and **36** have been achieved on the basis of this method.



INTRODUCTION

Prostaglandins (PGs) are a group of naturally occurring C_{20} substances found in trace amount in animals and men, which were once widely believed to be very promising therapeutic agents for a number of diseases.[1,2] Among them, prostaglandin E_2 (PGE_2, **1** in Figure 1) is the most well-known member that

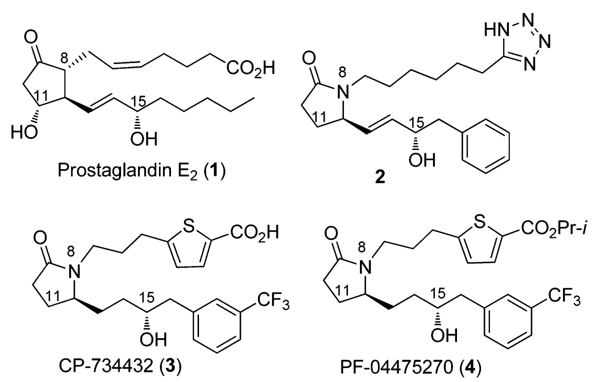


Figure 1. Prostaglandin E_2 (PGE_2) and pharmaceutically relevant 11-deoxy-8-aza-PGE_2 analogues.

exhibits a broad range of physiological activities. However, its development as the medicinal agent has been impeded due to its instability, quick metabolism and side effects.[1,2] To tackle these problems, many aza-analogues of PGE_2, in which a CH or a CH_2 of the cyclopentane ring is replaced by a nitrogen, have been synthesized.[3] Recently, γ-lactam analogue **2** has been revealed as a potent and selective agonist of the prostaglandin EP_4 receptor by Merck's recent receptor binding assays.[4] CP-734432 (**3**) has been discovered by Pfizer's high throughput screening as a highly selective EP_4 receptor agonist with an IC_{50} = 2 nM.[5] PF-4475270 (**4**), the isopropyl ester prodrug of **3**, was shown to be a novel ocular hypotensive compound capable of effectively lowering intraocular pressure in dogs.[6] Surprisingly, in spite of the great progress made in the chemistry and biochemistry of 8-aza-analogues of PGs,[7] only 8-aza-11-deoxyanalogues of PGs have so far been reported. In the light of the structure of PGE_2, it is worthwhile to develop 8-aza-analogues of PGE_2 with the 11-hydroxyl group retained.

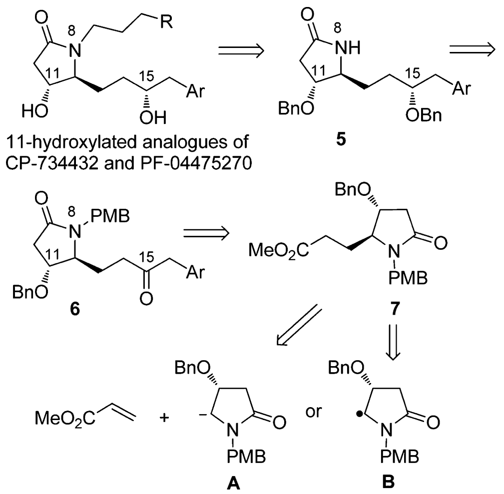
Our retrosynthetic analysis of 11-hydroxylated analogues of CP-734432 and PF-04475270 is depicted in Scheme 1, in which the retro-Michael addition type disconnection of lactam **7** is the key step, leading to either the carbanionic synthon **A** or the radical synthon **B**.

Carbon−carbon bond formation at the N-α-carbon is a fundamental transformation in the synthesis of nitrogen-containing compounds. Although many N-α-carbanion-based methodologies,[8] including that based on the Boc-stabilized α-(N-carbamoyl)alkylsamarium(III) species **C**,[9] have been documented, the C−C bond formation via the β-hydroxypyrrolidin-2-one-based N-α-carbanion of types **A** (Scheme 1) and **A1**/**A2** (Figure 2) remains challenging due to a lack of chelation

Special Issue: Howard Zimmerman Memorial Issue

Received: June 22, 2012

Scheme 1. Retrosynthetic Analysis of 11-Hydroxylated Analogues of CP-734432 and PF-04475270



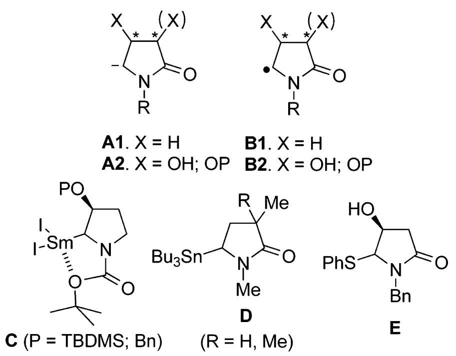


Figure 2. (4-Hydroxy)pyrrolidin-2-one N-α-carbanion/α-carba radical synthons and their precursors.

stabilization (cf. **D** in Figure 2),[10] poor nucleophilic reactivity toward electrophiles,[10b] the proton exchange with the lactam's acidic proton (cf. **E** in Figure 2),[10b,11] and/or the easy β-elimination.[12]

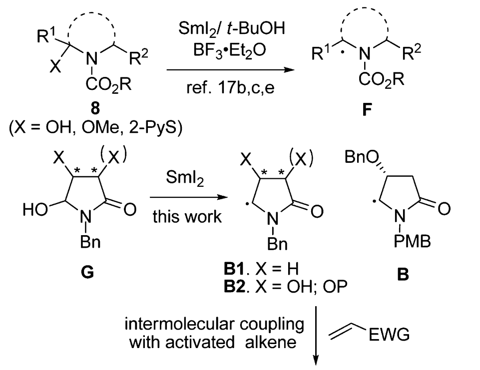
In this context, the α-acylaminoalkyl radicals-based C−C bond formation methodology pioneered by Hart[13] affords another complementary synthetic way.[14,15] β-Hydroxylated lactam N-α-alkyl radicals represented by **B1**/**B2** (Figure 2) have been used successfully in the total synthesis of hydroxylated alkaloids.[13a,e,15] However, the reported reactions of the lactam N-α-alkyl radicals were limited to the intramolecular version,[13,15] and the corresponding intermolecular reaction had not been reported. This raised concerns about the stability of the lactam N-α-alkyl radicals under the classic thermal conditions using AIBN/Bu_3SnH as a radical initiation/propagation system in benzene/toluene. In this regard, the SmI_2-based chemistry[16] pioneered by Kagan and co-workers provides a valuable solution to the problem, since such kind of radical reactions are generally run at mild conditions (−78 °C to rt).

To execute our synthetic plan displayed in Scheme 1, we intended to develop a SmI_2-based intermolecular coupling of γ-lactam N-α-alkyl radicals of type **B** in particular, and types **B1** and **B2** in general, with activated alkenes. The results of this research and application of the newly developed method to the asymmetric synthesis of 11-hydroxylated analogues of CP-734432 (**3**) and PF-04475270 (**4**) are reported herein.

■ RESULTS AND DISCUSSION

Previous to this work, we have embarked on a general program aiming at the development of SmI_2-based methodologies for the asymmetric synthesis of N-containing compounds.[17] In those studies, we have demonstrated that the α-acylaminoalkyl radicals of types **F** can be generated from the corresponding N-carbamoyl hemiaminals/N,O-acetals/N,S-acetals **8** through the action of SmI_2 under mild conditions (Scheme 2). We expected this

Scheme 2



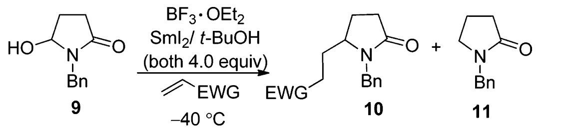
chemistry to be extended to the lactam hemiaminals **G**, thus allowing the generation of the γ-lactam N-α-alkyl radicals of types **B**, **B1** and **B2**, and the following intermolecular interception by activated alkenes.

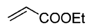
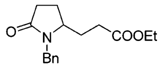
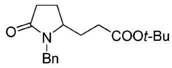
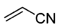
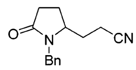
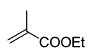
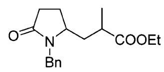
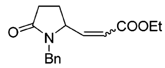
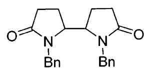
The radical coupling of γ-lactam-hemiaminal **9** was first investigated. According to our previously established conditions,[17e] compound **9** was successively treated with 2 mol equiv of $BF_3 \cdot OEt_2$, a solution of *tert*-butanol-containing SmI_2 in THF (0.1 M, 4 equiv), and an activated alkene at −40 °C (Table 1). As can be seen from Table 1, the coupling of γ-lactam-hemiaminal **9** with ethyl acrylate produced the desired product **10a** in 78% yield along with the reduced product **11**[18] in 10% yield (Table 1, entry 3). Under the same conditions, other activated alkenes reacted with γ-lactam-hemiaminal **9** (Table 1, entries 4 to 7) to give the corresponding products in 49−76% yields. To confirm the formation of the lactam N-α-alkyl radical intermediates, the reaction of γ-lactam-hemiaminal **9** in the absence of an activated alkene was carried out. The homocoupling[19d] product bipyrrolidin-2-one **10f** was isolated in 33% yield as a 1:1 mixture of *dl*- and *meso*-diastereomers, along with the reduced product **11** in 65% yield (Table 1, entry 8).

Encouraged by these results, the cross-coupling reaction of γ-lactam hemiaminal **12**, easily available from (S)-malic acid,[20a] was then investigated. However, under the above-mentioned optimized conditions, the reaction of γ-lactam-hemiaminal **12** with ethyl acrylate failed to afford the desired coupling product **15a** (Table 2, entry 1). Only 40% of **15a** was obtained, along with the known reduced side product **16**,[21] when the reaction was run at 0 °C (Table 2, entry 2). Use of other Lewis acids such as TMSOTf and Tf_2O, or lactam N,O-acetals such as **13**[20b] and **14**[22] did not lead to any improvement of the yields (Table 2, entries 3−6).

To tackle this problem, sulfide **17** and sulfone **18** were attempted (Scheme 3). The seminal work of Beau and Skrydstrup has nicely demonstrated the utility of glycosyl pyridyl sulfones in the samarium diiodide-mediated reductive coupling with ketones or aldehydes under Barbier conditions.[19] We have also realized similar coupling of (pyrid-2-yl)(pyrrolidin-2-yl-

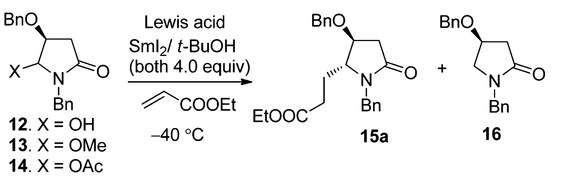
Table 1. SmI_2-Mediated Radical Coupling of γ-Lactam-hemiaminal 9 with Activated Alkenes



Entry	activated alkenes/ alkyne	Product **10** (% yield)[c] (d.r.)[d] and **11** (% yield)[c]
1		0[a]
2		 **10a** (41),[b] **9** (10), **11** (9)
3		**10a** (78), **11** (10)
4		 **10b** (76), **11** (8)
5		 **10c** (54), **11** (15)
6		 **10d** (73) (1.8 : 1), **11** (17)
7		 **10e** (49) (*Z* : *E* = 1.6 : 1),[e] **11** (30)
8.	none	 **10f** (33)[e] (1 : 1), **11** (65)

[a]In the absence of $BF_3·OEt_2$. [b]In the absence of *t*-BuOH. [c]Isolated yield. [d]Determined by HPLC analysis. [e]Yield not optimized.

Table 2. SmI_2-Mediated Reductive Coupling of γ-Lactam-hemiaminal 12 and γ-Lactam-*N,O*-acetals 13, 14 with Ethyl Acrylate

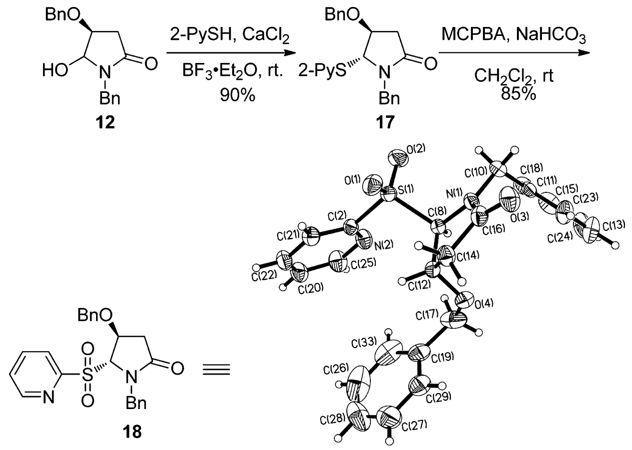


entry	starting material, Lewis acid (equiv)	*T* (°C)	products **15a** (% yield) and **16** (% yield)[a]	recovered starting material (%)[a]
1	**12**, $BF_3·OEt_2$ (2)	−40	none	100
2	**12**, $BF_3·OEt_2$ (2)	0	(40) and (40)	15
3	**12**, TMSOTf (1)	0	(16) and (16)	23
4	**13**, Tf_2O (1)	0	(35) and (0)	64
5	**13**, $BF_3·OEt_2$ (2)	0	(26) and (22)	17
6	**14**, $BF_3·OEt_2$ (1)	0	(31) and (19)	

[a]Isolated yield.

carbamate)sulfides with carbonyl compounds.[9] Recently, we have shown that with *t*-butanol as a proton source and in the presence of $BF_3·OEt_2$, the mechanism of SmI_2-mediated coupling reaction of sulfides can be switched from a Barbier type (via samarium(III) intermediates)[9] to a radical one (via *N*-carbamoyliminium ion intermediates).[17b]

Scheme 3. Preparation of Sulfide 17 and Sulfone 18 and the X-Ray Structure of 18



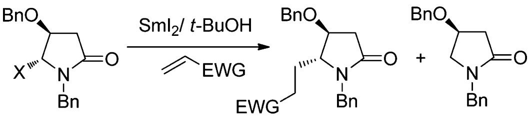
The requisite 2-pyridylsulfide **17** was first prepared by $BF_3·OEt_2$ (2.0 equiv)-catalyzed reaction of **12** with 2-mercaptopyridine, as a separable mixture of diastereomers in a 2:1 ratio (yield: 90%). The stereochemistry of the major diastereomer **17** was assigned as 4,5-*trans* according to the observed vicinal coupling constant[22] ($J_{4,5}$ = 0 Hz). It was observed that the *cis*-isomer gradually epimerized to the *trans*-isomer upon standing. Oxidation (MCPBA, $NaHCO_3$) of the diastereomeric mixture of the sulfides **17** and 5-*epi*-**17** afforded the 2-pyridylsulfone **18** with 85% yield in a nearly diastereomerically pure form, the stereochemistry of which was determined to be the 4,5-*trans* by both H^1 NMR ($J_{4,5}$ = 0 Hz) and single-crystal X-ray diffraction analysis (Scheme 3).

The cross-coupling of the sulfide **17** and sulfone **18** with activated alkenes was then examined, and the results are summarized in Table 3. As can be seen from entries 1 and 2, the coupling reactions of sulfide **17** with ethyl acrylate is effectively promoted by $BF_3·OEt_2$, improving the yield from 30 to 75%. The coupling reactions of sulfone **18**, however, underwent smoothly in the absence of $BF_3·OEt_2$ (entries 3, 5, 7, 9). Superior yields (75−90%) were obtained from cross-coupling reactions of sulfone **18** with activated alkenes compared with those with sulfide **17** (40−75%). Nevertheless, excellent 4,5-*trans*-diastereoselectivities were observed for both the sulfide **17** and sulfone **18**. The stereochemistry of the major products were assigned according to the observed vicinal coupling constants[22] ($J_{4,5}$ = 1.8−2.0 Hz). In the absence of an activated alkene, the homocoupling product **15e** was yielded as a single diastereomer in 21%, along with the reduced product **16** in 19%, and the elimination product **19** in 50% (Table 3, entry 10). The stereochemistry of homocoupling product **15e** was deduced from the observed vicinal coupling constants[22] ($J_{4,5}$ = 0 Hz; $J_{4,5}$ = 8.3 Hz). The formation of the homocoupling product **15e** implicated the involvement of a γ-lactam *N*-α-alkyl radical.

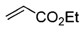
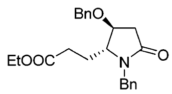
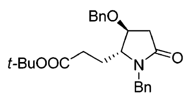
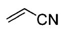
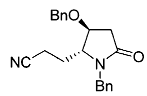
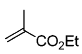
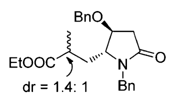
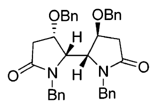
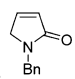
In light of the homocoupling products (**10f** and **15e**) formation, two plausible radical-based reaction mechanisms are depicted in Scheme 4. For the reaction of γ-lactam-hemiaminal **12** (and also hemiaminal **9**), route A is proposed, according to the imperative role played by the Lewis acid $BF_3·OEt_2$. The γ-lactam-iminium ion **H** is first generated in situ from γ-lactam-hemiaminal **12** under action of $BF_3·OEt_2$. A single electron reduction of the γ-lactam-iminium ion **H** by SmI_2 afforded the γ-

dx.doi.org/10.1021/jo301277n | J. Org. Chem. XXXX, XXX, XXX−XXX

Table 3. SmI_2-Mediated Reductive Coupling of Sulfide 17 and Sulfone 18 with Activated Alkenes

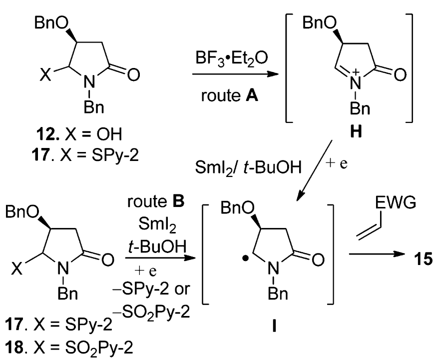


17. X= SPy-2
18. X= SO_2Py-2 | **15** | **16**

Entry	Starting material/ activated alkenes[a]			Product **15** (% yield)[c] (d.r.)[d,e] and **16** (% yield)[c]
1	**17**[a]			**15a** (30), **16** (25)
2	**17**[b]			**15a** (75) (single isomer), **16** (5)
3	**18**[a]			**15a** (90) (single isomer)
4	**17**[b]			**15b** (65) (single isomer), **16** (12)
5	**18**[a]			**15b** (75) (single isomer)
6	**17**[b]			**15c** (40), **16** (15)
7	**18**[a]			**15c** (75) (12 : 1)
8	**17**[b]			**15d** (60) (1.4 : 1), **16** (10)
9	**18**[a]			**15d** (77) (1.5:1)
10	**18**[a]	None		**15e** (21),[f] **16** (19),  **19** (50)

[a]**17** or **18** (1.0 equiv), an α,β-unsaturated compound (2.0 equiv) and t-BuOH (4.0 equiv) were dissolved in THF, a freshly prepared SmI_2 solution (4 mol equiv) in THF was added dropwise at −60 °C. [b]**17** (1.0 equiv), an α,β-unsaturated compound (2.0 equiv) and BF_3·OEt_2 (2.0 equiv) were dissolved in THF, a freshly prepared t-BuOH-containing (4 mol equiv) SmI_2 solution (4 mol equiv) in THF was added dropwise at −78 °C. [c]Isolated yield. [d]Ratio determined by HPLC analysis. [e]dr for the newly formed stereogenic center at the side chain. [f]Yield not optimized.

Scheme 4. Plausible Mechanisms of the Cross Coupling Reactions



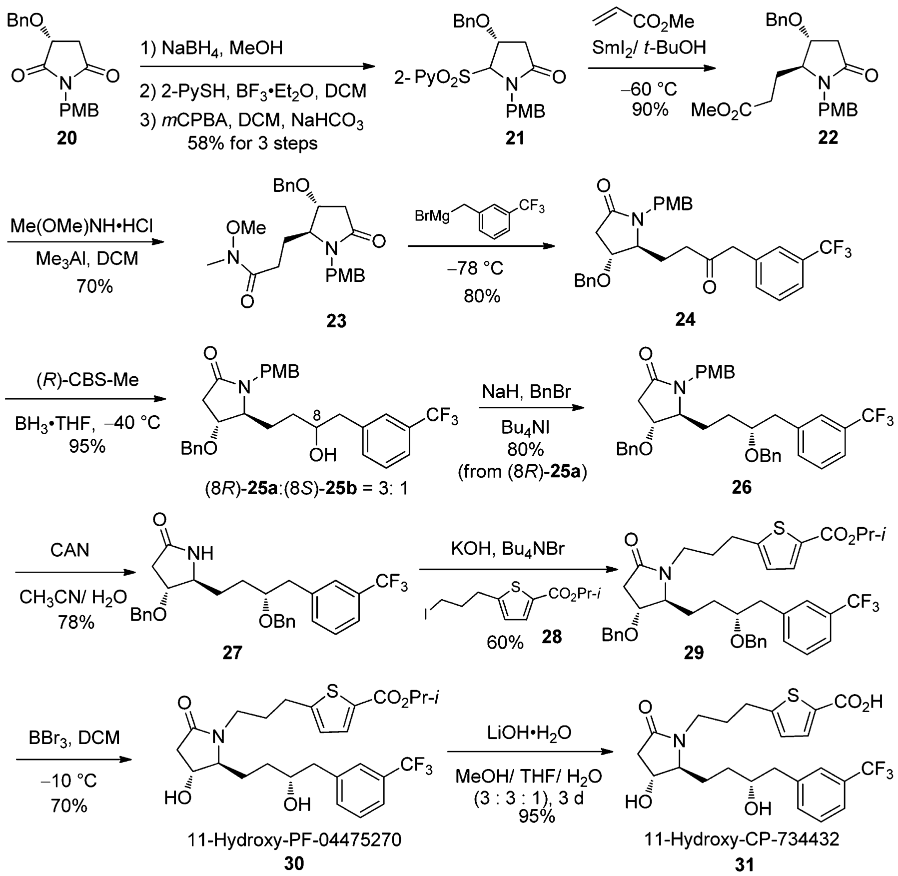
lactam N-α-alkyl radical **I**, which was trapped by an activated alkene to form a C−C bond at the γ-lactam N-α-carbon. For the reaction of sulfone **18**, based on the fact that BF_3·OEt_2 has no impact on the reaction, route B is proposed, in which the γ-lactam N-α-alkyl radical **I** is generated directly from sulfone **18** through the SmI_2-mediated homolytic cleavage of the C−S bond. For the reaction of sulfide **17**, both route A and B are involved, considering the improvement of the reaction yield by the use of BF_3·OEt_2. The high *trans*-diastereoselectivity in the coupling reactions of **17** and **18** can be ascribed to the 1,2-stereochemical induction by C-4 benzyloxy group. Such 1,2-stereochemical induction is well documented for both intermolecular[23] and intramolecular[13a,e] radical reactions under classic tin-based conditions (AIBN, Bu_3SnH, C_6H_6, reflux).

With the method for the generation and intermolecular coupling of the γ-lactam N-α-alkyl radicals **B** established, we next focused on the asymmetric synthesis of 8-aza-analogues of PGE_2. The novel 11-hydroxylated analogues of PF-04475270 (**30**), CP-734432 (**31**), **35** and **36** were selected as our targets.

The synthesis started from the γ-lactam 2-pyridyl sulfone **21**, which is easily prepared as a separable 4,5-*trans/cis* diastereomeric mixture in a 3:1 ratio (determined by ^{1}H NMR) in three steps with an overall yield of 58% from the known malimide[24] **20**. The observed $J_{4,5}$ = 0 Hz allowed assigned a 4,5-*trans*-stereochemistry for the major diastereomer of **21**. Although diastereomeric pure 2-pyridylsulfone **18** was used for the coupling reactions in our above-mentioned investigation, both diastereomers would give the same result according our

dx.doi.org/10.1021/jo301277n | J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 5. Asymmetric Synthesis of 11-Hydroxylated Analogues (30, 31) of PF-04475270 and CP-734432

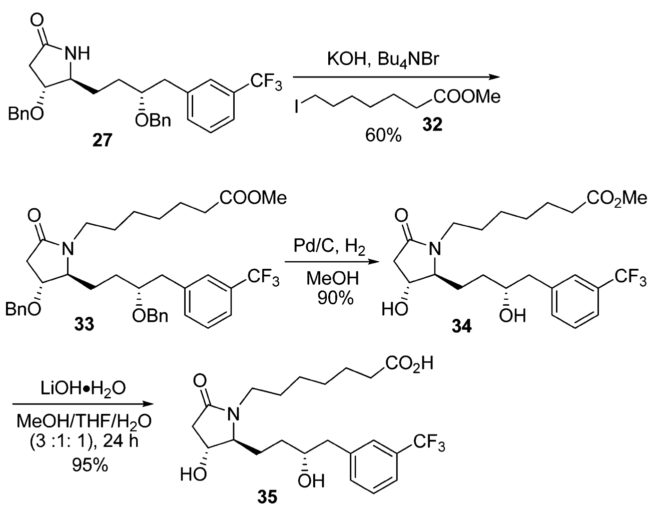


suggested radical mechanism. Indeed, the SmI_2-mediated cross coupling of the diastereomeric mixture of sulfone **21** with methyl acrylate in the presence of *t*-BuOH at −60 °C produced the desired coupling product **22** as the sole detectable diastereomer in 90% yield (determined by ^{1}H NMR of a crude sample). Ester **22** was converted into Weinreb amide[25] **23** in 70% yield, which reacted with (3-(trifluoromethyl)benzyl) magnesium bromide at −78 °C to give ketone **24** in 80% yield. Diastereoselective reduction of ketone **24** with Corey's methyl CBS oxazaborolidine reagents (*R*-Me CBS oxazaborolidine)[26] in combination with borane−dimethyl sulfide complex provided alcohol (8*R*/8*S*)-**25** as a separable diastereomeric mixture (*dr* = 3:1) in 95% yield. The C-8 stereochemistry of the minor diastereomer **25b** was determined to be 8*S* by the modified Mosher method,[27] and that of the major one **25a** was deduced to be 8*R*.

Protection of the hydroxyl group in **25a** gave benzyl ether **26** in 80% yield, which was subjected to oxidative cleavage with CAN in a mixed solvent system MeCN/H_2O (9:1, v/v, rt) to afford *γ*-lactam **27** in 78% yield. Treatment of *γ*-lactam **27** with isopropyl 5-(3-iodopropyl)thiophene-2-carboxylate **28**[7e] gave the *N*-alkylation product **29** in 60% yield. Exposure of compound **29** to BBr_3 in DCM at −10 °C allowed the cleavage of two benzyl groups to furnish our first target 11-hydroxy-PF-04475270 (**30**) in 70% yield. Saponification of compound **30** produced our second target molecule 11-hydroxy-CP-734432 (**31**) in 95% yield (Scheme 5).

For the synthesis of the third target molecule **35**, *γ*-lactam **27** was alkylated with iodide **32**,[28] which produced compound **33** in 60% yield (Scheme 6). Under catalytic hydrogenolytic conditions (H_2, 1 atm, 10% Pd/C, rt, 24 h), *O*,*O*′-bis-debenzylation underwent smoothly to give diol **34** in 90% yield. Saponification of the ester **34** yielded the target carboxylic acid **35** in 95% yield.

Scheme 6. Asymmetric Synthesis of 11-Hydroxylated Analogue 35



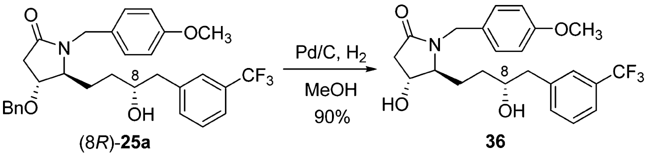
Finally, compound **36**, another aza-analogue of PF-4475270 (**30**)/CP-734432 (**31**), was obtained in 90% yield from compound (8*R*)-**25a** by catalytic hydrogenolysis (Scheme 7).

■ CONCLUSION

In conclusion, we have accomplished, for the first time, the intermolecular coupling reaction of the *γ*-lactam *N*-*α*-alkyl

dx.doi.org/10.1021/jo301277n | J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 7. Asymmetric Synthesis of 11-Hydroxylated Analogue 36



radicals of type **B**, **B1** and **B2** with activated alkenes. The easy availability of the substrates (γ-lactam-hemiaminal **9**, lactam 2-pyridyl sulfide **17** and lactam 2-pyridyl sulfones **18** and **21**) renders this efficient C−C bond formation a versatile methodology for the synthesis of 5-substituted γ-lactams, which is complementary to other SmI_2-based cross coupling methods.[9,16,17,29] Excellent *trans*-diastereoselectivities were observed in the coupling reactions of (*S*)-malimide derived lactam sulfide **17** and lactam sulfone **18**. Taking advantage of this method, we have accomplished the asymmetric synthesis of four 8-aza-analogues of PGE_2, namely, the 11-hydroxylated analogue of PF-04475270 (**30**), the 11-hydroxylated analogue of CP-734432 (**31**), compounds **35** and **36**. It is noteworthy that bi-γ-lactams **10f** and **15e** are ready precursors for the synthesis of potentially useful bipyrrolidine type chiral ligands.[30]

EXPERIMENTAL SECTION

(4*S*,5*R*)-1-Benzyl-4-benzyloxy-5-(pyridin-2-ylthio)pyrrolidin-2-one (17). To a mixture of the known hemiaminal **12** (1.00 g, 3.4 mmol) and $CaCl_2$ (753 mg, 6.8 mmol) and pyridine-2-thiol (564 mg, 5.1 mmol) in dry CH_2Cl_2 (15 mL) was added $BF_3{\cdot}Et_2O$ (0.42 mL, 3.4 mmol) at 0 °C under nitrogen atmosphere. After being stirred at room temperature for 5 h, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (2 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 1:2) to afford the less polar diastereomer **17** (660 mg, yield: 50%) and the more polar diastereomer (530 mg, yield: 40%). The sulfide **17** is a white solid: mp 78−79 °C (EtOAc/PE 1:2); $[\alpha]^{20}_{D}$ +1.6 (*c* 1.4, $CHCl_3$); IR (KBr) 3120, 3021, 1705, 1578, 1454, 1415, 1124, 1087, 1070, 759, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.47 (d, *J* = 17.6 Hz, 1H), 2.84 (dd, *J* = 5.2, 17.6 Hz, 1H), 3.98 (d, *J* = 15.2 Hz, 1H), 4.29 (d, *J* = 5.2 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 5.03 (d, *J* = 15.2 Hz, 1H), 5.63 (s, 1H), 6.88−6.97 (m, 1H), 7.04−7.29 (m, 11H), 7.37−7.45 (m, 1H), 8.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.4, 44.0, 67.7, 71.0, 78.6, 120.4, 123.4, 127.4 (2C), 127.7 (2C), 127.9 (2C), 128.4 (2C), 128.6 (2C), 136.0, 136.4, 137.8, 149.5, 156.8, 173.4; MS (ESI, *m*/*z*) 391 ($M + H^+$). Anal. Calcd for $C_{23}H_{22}N_2O_2S$: C, 70.74; H, 5.68; N, 7.17. Found: C, 70.34; H, 5.57; N, 7.07.

(4*S*,5*R*)-1-Benzyl-4-benzyloxy-5-(pyridin-2-ylsulfonyl)-pyrrolidin-2-one (18). To a solution of sulfide **17** (612 mg, 1.57 mmol) in CH_2Cl_2 (16 mL) was added $NaHCO_3$ (923 mg, 11.0 mmol) and MCPBA (70−75%, balance 3-chlorobenzoic acid and water) (1.13 g, 4.7 mmol) at 0 °C. After being stirred for 30 min at 0 °C and for 2 h at room temperature, the mixture was then diluted with CH_2Cl_2 (50 mL). The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (25 mL) and brine (25 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 1:2) to afford sulfone **18** (563 mg, yield: 85%) as white crystals: mp 123.0−123.2 °C (EtOAc/PE 1:2); $[\alpha]^{20}_{D}$ −3.3 (*c* 1.2, $CHCl_3$); IR (KBr) 3125, 3027, 1716, 1404, 1316, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.40 (d, *J* = 17.7 Hz, 1H), 2.72 (dd, *J* = 6.2, 17.7 Hz, 1H), 3.88 (d, *J* = 15.2 Hz, 1H), 4.28 (d, *J* = 11.6 Hz, 1H), 4.33 (d, *J* = 11.6 Hz, 1H), 4.65 (d, *J* = 6.2 Hz, 1H), 4.96 (s, 1H), 5.09 (d, *J* = 15.2 Hz, 1H), 6.98−7.03 (m, 2H), 7.03−7.09 (m, 2H), 7.15−7.23 (m, 6H), 7.52 (m, 1H), 7.88 (m, 1H), 7.93−7.98 (m, 1H), 8.62−8.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.3, 45.4, 70.9, 72.5, 79.8, 123.8, 127.6, 127.8, 127.9, 128.0 (2C), 128.2 (2C), 128.4 (2C), 128.7 (2C), 134.6, 136.4, 138.6, 150.5, 155.7, 174.2; MS (ESI, *m*/*z*) 423 ($M + H^+$). Anal. Calcd for $C_{23}H_{22}N_2O_4S$: C, 65.38; H, 5.25; N, 6.63; S, 7.59. Found: C, 65.30; H, 5.33;.N, 6.59; S, 7.46.

Preparation of the *t*-BuOH-Containing SmI_2 Solution in THF. To a slurry of Sm powder (flame-dried under Ar, 826 mg, 5.5 mmol) in anhydrous THF (50 mL) was added I_2 (1.27 g, 5.0 mmol) at room temperature under an argon atmosphere. The reaction mixture was stirred for 2 h at 45 °C to yield a dark blue SmI_2 (0.1 N in THF) reagent. To the resulting mixture was added *t*-BuOH (0.43 mL, 5.0 mmol), and the mixture was stirred for 10 min to yield a *t*-BuOH-containing SmI_2 (both 0.1 M in THF).

General Procedure for the Cross-Coupling of Lactam-Hemiaminal with Activated Alkenes. *Protocol A.* To a solution of hemiaminal **9** or sulfide **17** (0.5 mmol), an activated alkene (1.0 mmol) and $BF_3{\cdot}Et_2O$ (2.0 mmol) in dry THF (10 mL) was dropwise added a freshly prepared *t*-BuOH-containing SmI_2 (both 0.1 M in THF, 20 mL, 2.0 mmol) at −40 or −78 °C. After being stirred for 10 min, the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL), and the resulting mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired cross-coupling product. In some cases, the reduced product was isolated as a side product.

Protocol B. To a solution of sulfone **18** (0.5 mmol) and an activated alkene (1.0 mmol) in dry THF (10 mL) was dropwise added a freshly prepared *t*-BuOH-containing SmI_2 (both 0.1 M in THF, 20 mL, 2.0 mmol) at −60 °C. After being stirred for 10 min, the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL), and the resulting mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired cross-coupling product. In some cases, the reduced product was isolated as a side product.

1-Benzyl-5-[2-(ethyloxycarbonyl)ethyl]-pyrrolidin-2-one (10a). Following the general **protocol A**, the SmI_2 mediated cross-coupling of hemiaminal **9** with ethyl acrylate afforded **10a** in 78% yield as a colorless oil: IR (film) 3029, 2979, 2936, 1732, 1682, 1445, 1420, 1183 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.1 Hz, 3H), 1.61−1.74 (m, 2H), 2.00−2.15 (m, 2H), 2.15−2.32 (m, 2H), 2.34−2.54 (m, 2H), 3.42−3.52 (m, 1H), 3.98 (d, *J* = 15.0 Hz, 1H), 4.00 (q, *J* = 7.1 Hz, 2H), 4.98 (d, *J* = 15.0 Hz, 1H), 7.18−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 23.3, 27.6, 29.2, 29.9, 43.9, 55.8, 60.4, 127.3 (2C), 127.8 (2C), 128.5, 136.4, 172.5, 174.8; MS (ESI, *m*/*z*) 276 ($M + H^+$); HRESIMS calcd for $[C_{16}H_{21}NO_3Na]^+$ ($M + Na^+$) 298.1400, found 298.1404.

1-Benzyl-5-[2-(*tert*-butyloxycarbonyl)ethyl]-pyrrolidin-2-one (10b). Following the general **protocol A**, the SmI_2 mediated cross-coupling of hemiaminal **9** with *tert*-butyl acrylate afforded **10b** in 76% yield as a colorless oil: IR (film) 2972, 2927, 1726, 1683, 1494, 1418 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 9H), 1.50−1.63 (m, 2H), 1.88−1.98 (m, 1H), 1,98−2.16 (m, 3H), 2.25−2.46(m, 2H), 3.36 (tdd, *J* = 3.1, 5.2, 8.3 Hz, 1H), 3.90 (d, *J* = 15.1 Hz, 1H), 4.90 (d, *J* = 15.1 Hz, 1H), 7.12−7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 27.8, 27.9 (9C), 30.0, 30.5, 44.0, 56.0, 80.7, 127.4, 128.0 (3C), 128.6 (2C), 136.6, 171.9, 174.9; MS (ESI, *m*/*z*) 304 ($M + H^+$, 100%). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.25; H, 8.00; N, 4.95.

1-Benzyl-5-(2-cyanoethyl)-pyrrolidin-2-one (10c). Following the general **protocol A**, the SmI_2 mediated cross-coupling of hemiaminal **9** with acrylonitrile afforded **10c** in 54% yield as a colorless oil: IR (film) 2932, 2869, 2240, 1674, 1497, 1446, 1417 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.63−1.75 (m, 2H), 1.96−2.06 (m, 1H), 2.13−2.21 (m, 1H), 2.22−2.32 (m, 2H), 2.37−2.55 (m, 2H), 3.56 (tdd, *J* = 3.1, 5.4, 8.5 Hz, 1H), 4.30 (d, *J* = 15.1 Hz, 1H), 4.90 (d, *J* = 15.1 Hz, 1H), 7.18−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 23.1, 28.4, 29.6, 44.3, 55.8, 118.5, 127.5, 127.6 (2C), 128.6 (2C), 136.1, 174.7; MS (ESI, *m/z*) 229 (M + H$^+$, 100%). Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.59; H, 7.10; N, 12.48.

1-Benzyl-5-[2-(ethyloxycarbonyl)propyl]-pyrrolidin-2-one (10d). Following the general **protocol A**, the SmI_2 mediated cross-coupling of hemiaminal **9** with ethyl methacrylate afforded **10d-H** (less polar diastereomer) in 27% yield and **10d-L** (more polar diastereomer) in 46% yield.

10d-H. Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, *J* = 6.9 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.64−1.85 (m, 3H), 2.03−2.15 (m, 1H), 2.33−2.46 (m, 2H), 2.47−2.58 (m, 1H), 3.38−3.49 (m, 1H), 3.92 (d, *J* = 15.1 Hz, 1H), 4.05−4.18 (m, 2H), 5.02 (d, *J* = 15.1 Hz, 1H), 7.18−7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 17.2, 23.9, 30.0, 35.8, 36.5, 44.0, 55.0, 60.7, 127.5 (2C), 128.0 (2C), 128.6, 136.5, 174.9, 176.0.

10d-L. Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (d, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.2 Hz, 3H), 1.23−1.32 (m, 1H), 1.61−1.70 (m, 1H), 2.07−2.25 (m, 2H), 2.32−2.54 (m, 3H), 3.32−3.41 (m, 1H), 3.95−4.08 (m, 2H), 4.02 (d, *J* = 15.0 Hz, 1H), 4.95 (d, *J* = 15.0 Hz, 1H), 7.22−7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.5, 24.2, 29.9, 36.2, 37.2, 44.1, 55.4, 60.5, 127.4 (2C), 128.1 (2C), 128.6, 136.7, 174.8, 175.5.

10d. Data: IR (film) 3028, 2982, 2921, 1729, 1688, 1417, 1255, 1188 cm^{-1}; MS (ESI, *m/z*) 290 (M + H$^+$). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.24; H, 7.66; N, 5.08.

(*E*) and (*Z*)-1-Benzyl-5-[2-(ethyloxycarbonyl)ethenyl]-pyrrolidin-2-one (10e). Following the general **protocol A**, the SmI_2 mediated cross-coupling of hemiaminal **9** with ethyl propiolate afforded **10e** as an inseparable diastereomeric mixture (*E*:*Z* = 1.6:1) in a combined yield of 49% as a colorless oil: IR (film) 3020, 2983, 2927, 1718, 1693, 1414, 1190, 1037 cm^{-1}; MS (ESI, *m/z*) 274 (M + H$^+$). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.04; H, 6.89; N, 5.48.

(Z)-***10e-H***. Less polar diastereomer, data read from spectrum of the diastereomeric mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.1 Hz, 3H), 1.67−1.79 (m, 1H), 2.30−2.58 (m, 3H), 4.05 (d, *J* = 14.8 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 4.79 (d, *J* = 14.8 Hz, 1H), 5.14−5.22 (m, 1H), 5.83 (dd, *J* = 1.0, 11.5 Hz, 1H), 6.02 (dd, *J* = 9.1, 11.5 Hz, 1H), 7.18−7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 24.8, 30.0, 45.2, 55.2, 60.4, 122.2, 127.4, 128.3, 128.4, 136.5, 148.0, 165.2, 175.0.

(E)-***10e-L***. More polar diastereomer, data read from spectrum of the diastereomeric mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.1 Hz, 3H), 1.79−1.88 (m, 1H), 2.16−2.27 (m, 1H), 2.42−2.58 (m, 2H), 3.82 (d, *J* = 14.8 Hz, 1H), 4.00−4.15 (m, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 5.03 (d, *J* = 14.8 Hz, 1H), 5.86 (dd, *J* = 0.8, 15.6 Hz, 1H), 6.72 (dd, *J* = 8.2, 15.6 Hz, 1H) 7.18−7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 24.6, 29.5, 44.6, 57.9, 60.7, 123.4, 127.6, 128.3, 128.7, 136.1, 145.8, 165.5, 174.7.

1,1′-Dibenzyl-2,2′-bipyrrolidine-5,5′-dione (10f). Following the general **protocol A** (in the absence of an *α*,*β*-unsaturated compound), the SmI_2-mediated homocoupling of hemiaminal **9** afforded **10f-H** (less polar diastereomer) in 16.5% yield and **10f-L** (more polar diastereomer) in 16.5% yield, along with the reduced product **11** in 65% yield.

10f-H. Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61−1.73 (m, 2H), 2.00−2.12 (m, 2H), 2.42−2.54 (m, 4H), 3.50 (d, *J* = 15.3 Hz, 2H), 3.73 (dd, *J* = 4.9, 8.5 Hz, 2H), 5.19 (d, *J* = 15.3 Hz, 2H), 7.05−7.11 (m, 4H), 7.24−7.36 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0 (2C), 29.8 (2C), 44.9 (2C), 57.1 (2C), 127.7 (3C), 127.8 (4C), 128.8 (3C), 135.7 (2C), 175.8 (2C).

10f-L. White solid: mp 133.4−134.4 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56−1.78 (m, 4H), 2.35−2.53 (m, 4H), 3.72−3.80 (m, 2H), 3.78 (d, *J* = 14.8 Hz, 2H), 4.81 (d, *J* = 14.8 Hz, 2H), 6.93−7.06 (m, 4H), 7.23−7.33 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0 (2C), 30.0 (2C), 44.9 (2C), 56.0 (2C), 127.7 (3C), 128.1 (4C), 128.7 (3C), 135.7 (2C), 175.1 (2C).

10f. Data: IR (KBr) 3018, 2921, 1686, 1408, 1250 cm^{-1}; MS (ESI, *m/z*) 349 (M + H$^+$). Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 76.14; H, 7.28; N, 8.27.

(4*S*,5*R*)-1-Benzyl-4-benzyloxy-5-[2-(ethyloxycarbonyl)ethyl]-pyrrolidin-2-one (15a). Following the general **protocol B**, the SmI_2-mediated cross-coupling of sulfone **18** with ethyl acrylate afforded **15a** in 90% yield as a colorless oil: $[\alpha]^{20}_D$ +41.3 (*c* 1.2, $CHCl_3$); IR (film) 3022, 2931, 1733, 1695, 1456, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.2 Hz, 3H), 1.59−1.70 (m, 1H), 1.95−2.05 (m, 1H), 2.15−2.31 (m, 2H), 2.54 (dd, *J* = 2.4, 17.6 Hz, 1H), 2.74 (ddd, *J* = 0.8, 6.4, 17.6 Hz, 1H), 3.49 (ddd, *J* = 2.0, 3.2, 8.8 Hz, 1H), 3.86 (ddd, *J* = 2.0, 2.4, 6.4 Hz, 1H), 3.98 (d, *J* = 15.2 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 5.05 (d, *J* = 15.2 Hz, 1H), 7.19−7.39 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 25.7, 29.5, 37.1, 43.9, 60.6, 62.1, 70.5, 75.4, 127.4, 127.5 (2C), 127.8 (2C), 127.9 (2C), 128.4 (2C), 128.6, 136.0, 137.2, 172.3, 172.4; MS (ESI *m/z*) 382 (M + H$^+$). Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.38; H, 7.30; N, 3.58.

(4*S*,5*R*)-1-Benzyl-4-Benzyloxy-5-[2-(*tert*-butyloxycarbonyl)-ethyl]-pyrrolidin-2-one (15b). Following the general **protocol B**, the SmI_2-mediated cross-coupling of sulfone **18** with *tert*-butyl acrylate afforded **15b** in 75% yield as a colorless oil: $[\alpha]^{20}_D$ +34.7 (*c* 1.2, $CHCl_3$); IR (film) 3125, 3030, 1725, 1693, 1406, 1148 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H), 1.53−1.65 (m, 1H), 1.90−2.01 (m, 1H), 2.06−2.23 (m, 2H), 2.52 (dd, *J* = 2.0, 17.5 Hz, 1H), 2.73 (dd, *J* = 6.5, 17.5 Hz, 1H), 3.49 (ddd, *J* = 1.8, 3.0, 9.2 Hz, 1H), 3.85 (ddd, *J* = 1.8, 2.0, 6.5 Hz, 1H), 3.98 (d, *J* = 15.2 Hz, 1H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 5.04 (d, *J* = 15.2 Hz, 1H), 7.18−7.34 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 27.8 (3C), 30.6, 37.1, 43.8, 62.1, 70.3, 75.3, 80.7, 127.3 (2C), 127.4 (2C), 127.7 (2C), 128.3 (2C), 128.5 (2C), 136.0, 137.2, 171.5, 172.3; MS (ESI, *m/z*) 410 (M + H$^+$). Anal. Calcd for $C_{25}H_{31}NO_4$: C, 73.32; H, 7.63; N, 3.42. Found: C, 73.48; H, 7.92; N, 3.58.

(4*S*,5*R*)-1-Benzyl-4-benzyloxy-5-(2-cyanoethyl)-pyrrolidin-2-one (15c). Following the general **protocol B**, the SmI_2-mediated cross-coupling of sulfone **18** with acrylonitrile afforded (4*S*, 5*S*)-**15c** (less polar diastereomer) in 6% yield and (4*S*,5*R*)-**15c** (more polar diastereomer) in 69% yield.

(4S,5R)-***15c-L***. Colorless oil: $[\alpha]^{20}_D$ +45.9 (*c* 1.0, $CHCl_3$); IR (film) 3031, 2930, 2250, 1692, 1448, 1356, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58−1.68 (m, 1H), 1.94−2.03 (m, 1H), 2.11−2.28 (m, 2H), 2.55 (dd, *J* = 3.4, 17.4 Hz, 1H), 2.77 (dd, *J* = 6.8, 17.4 Hz, 1H), 3.52 (ddd, *J* = 3.0, 3.0, 9.4 Hz, 1H), 3.91 (ddd, *J* = 3.0, 3.4, 6.8 Hz, 1H), 4.06 (d, *J* = 15.3 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.93 (d, *J* = 15.3 Hz, 1H), 7.20−7.50 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 26.9, 37.0, 44.4, 62.0, 70.9, 75.2, 118.5, 127.7 (2C), 127.8 (2C), 128.1 (2C), 128.6 (2C), 128.9 (2C), 135.7, 136.9, 172.2; MS (ESI, *m/z*) 335 (M + H$^+$). Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.04; H, 6.85; N, 8.22.

(4*S*,5*R*)-1-Benzyl-4-benzyloxy-5-[2-(ethyloxycarbonyl)-propyl]pyrrolidin-2-one (15d). Following the general **protocol B**, the SmI_2-mediated cross-coupling of sulfone **18** with ethyl methacrylate afforded **15d-H** (less polar diastereomer) in 31% yield and **15d-L** (more polar diastereomer) in 46% yield.

15d-H. Colorless oil: $[\alpha]^{20}_D$ +65.2 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, *J* = 7.0 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.62 (ddd, *J* = 3.7, 7.0, 14.2 Hz, 1H), 1.83 (ddd, *J* = 7.0, 8.9, 14.2 Hz, 1H), 2.33−2.43 (m, 1H), 2.54 (dd, *J* = 2.1, 17.5 Hz, 1H), 2.78 (dd, *J* = 6.4, 17.5 Hz, 1H), 3.48 (ddd, *J* = 1.6, 3.7, 8.9 Hz, 1H), 3.89 (d, *J* = 15.4 Hz, 1H), 3.89 (ddd, *J* = 1.6, 2.1, 6.4 Hz, 1H), 4.02−4.15 (m, 2H), 4.37 (d, *J* = 11.7 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 5.09 (d, *J* = 15.4 Hz, 1H), 7.12−7.40 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 17.6, 34.6, 36.0, 37.2, 43.9, 60.8, 61.1, 70.5, 76.2, 127.5 (2C), 127.8 (3C), 128.4 (3C), 128.6 (2C), 136.0, 137.3, 172.5, 175.7.

15d-L. Colorless oil: $[\alpha]^{20}_D$ +21.0 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.22 (ddd, *J* = 3.4, 11.0, 14.0 Hz, 1H), 2.09 (ddd, *J* = 2.8, 11.2, 14.0 Hz, 1H), 2.38−2.48 (m, 1H), 2.51 (dd, *J* = 1.7, 17.5 Hz, 1H), 2.73 (ddd, *J* = 6.2, 17.4 Hz, 1H), 3.44 (ddd, *J* = 1.1, 2.8, 11.0 Hz, 1H), 3.83 (ddd, *J* = 1.1, 1.7, 6.2 Hz, 1H), 3.97 (d, *J* = 15.2 Hz, 1H), 3.99 (q, *J* = 7.1 Hz, 2H), 4.38 (d, *J* = 12.4 Hz, 1H), 4.42 (d, *J* = 12.4 Hz, 1H), 5.04 (d, *J* = 15.2 Hz, 1H), 7.19−7.35 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 18.5, 34.6, 36.1, 37.0, 43.9, 60.6, 61.1, 70.2, 75.6, 127.4, 127.5 (2C), 127.8 (2C), 128.0 (2C), 128.4 (2C), 128.5, 136.2, 137.4, 172.3, 175.4.

15d. Data: IR (film) 3046, 2978, 2934, 1730, 1695, 1455, 1161, 1092, 1028 cm^{-1}; MS (ESI, m/z) 396 (M + H^+). Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.55; H, 7.74; N, 3.62.

(2*S*,2′*R*,3*S*,3′*S*)-1,1′-dibenzyl-3,3′-bis(benzyloxy)-2,2′-bipyrrolidin-5,5′-dione (15e). Following the general **protocol B** (in the absence of an α,β-unsaturated compound), the SmI_2-mediated homocoupling of sulfone **18** afforded **15e** in 21% yield, along with the reduced product **16** in 9% yield and the elimination product **19** in 50% yield.

15e. Colorless oil: $[\alpha]^{20}_{D}$ −7.9 (c 1.0, $CHCl_3$); IR (film) 3029, 1689, 1404, 1092 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (dd, J = 9.5, 16.8 Hz, 1H), 2.55 (d, J = 17.8 Hz, 1H), 2.64−2.76 (m, 2H), 3.44 (d, J = 15.1 Hz, 1H), 3.50 (d, J = 15.5 Hz, 1H), 3.79 (dd, J = 1.3, 8.3 Hz, 1H), 3.98 (s, 1H), 4.03 (d, J = 6.1 Hz, 1H), 4.18 (d, J = 11.3 Hz, 1H), 4.26 (d, J = 11.8 Hz, 1H), 4.22−4.30 (m, 1H), 4.33 (d, J = 11.8 Hz, 1H), 4.36 (d, J = 11.3 Hz, 1H), 5.31 (d, J = 15.1 Hz, 1H), 5.33 (d, J = 15.5 Hz, 1H), 6.91−7.31 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.9, 38.5, 44.3, 45.3, 56.6, 62.6, 70.1, 72.4, 72.8, 73.0, 127.3, 127.6 (2C), 127.7 (2C), 127.8 (2C), 127.9 (2C), 128.07 (2C), 128.12 (2C), 128.2 (2C), 128.5 (2C), 128.8 (2C), 128.9, 135.0, 135.3, 136.3, 137.4, 171.9, 173.8; MS (ESI, m/z) 561 (M + H^+). Anal. Calcd for $C_{36}H_{36}N_2O_4$: C, 77.12; H, 6.47; N, 5.00. Found: C, 76.95; H, 6.10; N, 4.80.

1-Benzyl-1H-pyrrol-2(5H)-one (19). Yellow oil: IR (film) 3124, 3030, 1678, 1404 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (t, J = 2.3 Hz, 2H), 4.53 (s, 2H), 5.16−5.20 (dt, J = 5.0, 2.3 Hz, 1H), 6.21−6.25 (dt, J = 5.0, 2.3 Hz, 1H), 7.12−7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.2, 45.4, 104.3, 127.5 (2C), 127.6 (2C), 128.6, 132.5, 136.6, 176.7; MS (ESI, m/z) 174 (M + H^+). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.23; H, 6.12; N, 7.76.

(*R*)-1-(4-Methoxybenzyl)-4-benzyloxy-5-(pyridin-2-ylthio)-pyrrolidin-2-one (21a). To a solution of (R)-1-(4-methoxybenzyl)-3-(benzyloxy)pyrrolidine-2,5-dione (1.00 g, 3.1 mmol) in MeOH (68 mL) was added $NaBH_4$ (351 mg, 9.2 mmol) at −15 °C with intensive stirring, and 30 min later another $NaBH_4$ (234 mg, 6.2 mmol) was added. After being intensively stirred for another 15 min, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL), and the resulting mixture was extracted with cooled CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the crude aza-hemiacetal was obtained as white solid, which could be used without further purification. To the mixture of the crude aza-hemiacetal, $CaCl_2$ (684 mg, 6.2 mmol) and pyridine-2-thiol (513 mg, 4.6 mmol) in dry CH_2Cl_2 (25 mL) was added $BF_3{\cdot}Et_2O$ (0.38 mL, 3.1 mmol) under nitrogen atmosphere at 0 °C. After being stirred at room temperature for 5 h, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (2 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 1:2) to afford **21a** as a diastereomeric mixture (diastereomeric ratio: 3:1, determined by the integral of by ^{1}H NMR) in a combined yield (828 mg, 64%) as a yellow oil: IR (film) 3030, 1705, 1578, 1454, 1415, 1124, 1087, 1070, 759, 698 cm^{-1}; MS (ESI, m/z) 421 (M + H^+); HRESIMS calcd for $[C_{24}H_{24}N_2O_3SNa]^+$ (M + Na^+) 443.1400, found 443.1404.

More polar diastereomer (data read from spectrum of the diastereomeric mixture): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (d, J = 17.6 Hz, 1H), 2.94 (dd, J = 6.0, 17.6 Hz, 1H), 3.80 (s, 3H), 4.02 (d, J = 14.8 Hz, 1H), 4.38 (d, J = 6.0 Hz, 1H), 4.59 (d, J = 11.6 Hz, 1H), 4.75 (d, J = 11.6 Hz, 1H), 5.07 (d, J = 14.8 Hz, 1H), 5.72 (s, 1H), 6.83 (d, J = 8.8 Hz, 2H), 7.05−7.07 (m, 2H), 7.18−7.32 (m, 7H), 7.50−7.54 (m, 1H), 8.36−8.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.3, 43.4, 55.1, 67.4, 70.8, 78.5, 113.8 (2C), 120.2, 123.2, 127.5, 127.6, 127.7 (2C), 128.2 (2C), 129.2 (2C), 136.3, 137.7, 149.3, 156.7, 158.9, 173.2.

Less polar diastereomer (data read from spectrum of the diastereomeric mixture): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (dd, J = 16.8, 8.4 Hz, 1H), 2.72 (dd, J = 16.8, 7.6 Hz, 1H), 3.80 (s, 3H), 3.96 (d, J = 14.8 Hz, 1H), 4.42−4.45 (m, 1H), 4.44 (d, J = 11.6 Hz, 1H), 4.63 (d, J = 11.6 Hz, 1H), 4.99 (d, J = 14.8 Hz, 1H), 6.31 (d, J = 6.0 Hz, 1H), 6.79 (d, J = 8.8 Hz, 2H), 7.05−7.07 (m, 2H), 7.18−7.32 (m, 7H), 7.50−7.54 (m, 1H), 8.36−8.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.7, 43.3, 55.1, 68.0, 71.7, 73.0, 113.7 (2C), 120.2, 123.6, 127.5, 127.6, 127.9 (2C), 128.2 (2C), 129.5 (2C), 136.3, 137.1, 149.1, 156.8, 158.8, 170.9.

(*R*)-1-(4-Methoxybenzyl)-4-benzyloxy-5-(pyridin-2-ylsulfonyl)pyrrolidin-2-one (21). A solution of **21a** (1.00 g, 2.4 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C, to which was added $NaHCO_3$ (1.4 g, 16.7 mmol) and MCPBA (70−75%, balance 3-chlorobenzoic acid and water) (1.20 g, 7.1 mmol). After being stirred for 30 min at 0 °C and for 4 h at room temperature, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (25 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 1:2) to afford **21** (968 mg) as a diastereomeric mixture (diastereomeric ratio: 3:1, determined by the integral of ^{1}H NMR) in a combined yield of 90%. Yellow oil: IR (film) 3125, 3027, 1716, 1404, 1316, 1108 cm^{-1}; MS (ESI, m/z) 453 (M + H^+); HRESIMS calcd for $[C_{24}H_{24}N_2O_5SNa]^+$ (M + Na^+) 475.1304, found 475.1309.

More polar diastereomer (data read from spectrum of the diastereomeric mixture): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (d, J = 17.6 Hz, 1H), 2.79 (dd, J = 6.0, 17.6 Hz, 1H), 3.80 (s, 3H), 3.88 (d, J = 15.2 Hz, 1H), 4.37 (d, J = 11.6 Hz, 1H), 4.41 (d, J = 11.6 Hz, 1H), 4.72 (d, J = 6.0 Hz, 1H), 5.03 (s, 1H), 5.14 (d, J = 15.2 Hz, 1H), 6.81−6.92 (m, 2H), 7.07−7.11 (m, 3H), 7.23−7.29 (m, 4H), 7.62−7.66 (m, 1H), 8.00−8.08 (m, 2H), 8.76−8.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.4, 44.9, 55.1, 70.9, 72.5, 79.6, 114.2 (2C), 123.9, 126.5, 127.4, 127.7 (2C), 128.0 (2C), 128.3 (2C), 130.2, 136.4, 138.6, 150.5, 155.6, 159.2, 174.1.

Less polar diastereomer (data read from spectrum of the diastereomeric mixture): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (dd, J = 8.0, 16.0 Hz, 1H), 2.95 (dd, J = 16.0, 10.0 Hz, 1H), 3.83 (s, 3H), 4.07 (d, J = 11.2 Hz, 1H), 4.17 (d, J = 11.2 Hz, 1H), 4.18−4.24 (m, 1H), 4.36 (d, J = 14.4 Hz, 1H), 5.31 (d, J = 14.4 Hz, 1H), 5.36 (d, J = 6.8 Hz, 1H), 6.81−6.92 (m, 2H), 7.07−7.11 (m, 3H), 7.23−7.29 (m, 4H), 7.62−7.66 (m, 1H), 8.00−8.08 (m, 2H), 8.76−8.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.0, 45.2, 55.1, 72.2, 73.7, 74.9, 114.1 (2C), 122.6, 126.5, 127.0, 127.6 (2C), 127.9 (2C), 128.2 (2C), 129.6, 136.1, 137.6, 149.3, 155.1, 158.2, 172.1.

(4*R*,5*S*)-1-(4-Methoxybenzyl)-4-benzyloxy-5-[2-(Methyloxycarbonyl)ethyl]-pyrrolidin-2-one (22). Following the general **protocol B**, the SmI_2-mediated cross-coupling of **21** with ethyl acrylate afforded **22** in 90% yield as a colorless oil: $[\alpha]^{20}_{D}$ −34.7 (c 1.4, $CHCl_3$); IR (film) 3031, 2928, 1736, 1689, 1513, 1246, 1090 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65−1.68 (m, 1H), 2.00−2.02 (m, 1H), 2.22−2.28 (m, 2H), 2.52 (dd, J = 2.4, 17.6 Hz, 1H), 2.74 (dd, J = 6.4, 17.6 Hz, 1H), 3.47 (dt, J = 8.4, 2.4 Hz, 1H), 3.65 (s, 3H), 3.79 (s, 3H), 3.85 (dt, J = 6.4, 2.4 Hz, 1H), 3.91 (d, J = 15.2 Hz, 1H), 4.38 (d, J = 12.0 Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 5.00 (d, J = 15.2 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 7.19−7.35 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 29.4, 37.3, 43.5, 51.8, 55.2, 62.1, 70.6, 75.5, 114.1 (2C), 127.6. 127.9 (2C), 128.1 (2C), 128.5 (2C), 129.3, 137.3, 159.0, 172.4, 172.9; HRESIMS calcd for $[C_{23}H_{27}NO_5Na]^+$ (M + Na^+) 420.1781, found 420.1781.

(4*R*,5*S*)-1-(4-Methoxybenzyl)-4-benzyloxy-5-[2-(*N*-methoxy-*N*-methylaminocarbonyl)ethyl]pyrrolidin-2-one (23). To a solution of N,O-dimethylhydroxylamine hydrochloride (84 mg, 0.51 mmol) in CH_2Cl_2 (4.5 mL) was added Me_3Al (0.51 mL of a 1 M solution in toluene, 0.51 mmol) dropwise at 0 °C. After stirring for 1 h, a solution of **22** (100 mg, 0.17 mmol) in CH_2Cl_2 (3 mL) was added. After being stirred for 24 h at room temperature, the reaction was quenched with a saturated aqueous solution of $KHSO_4$ (2 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/PE 2:1) to afford **23** (113 mg, yield: 70%) as a colorless oil: $[\alpha]^{20}_{D}$ −22.1 (c 1.4, $CHCl_3$); IR (film) 3030, 2923, 1686, 1664, 1513, 1246, 1030 cm^{-1}; ^{1}H

NMR (400 MHz, $CDCl_3$) δ 1.64−1.73 (m, 1H), 2.03−2.04 (m, 1H), 2.34−2.36 (m, 2H), 2.52 (d, *J* = 17.2 Hz, 1H), 2.75 (dd, *J* = 6.4, 17.2 Hz, 1H), 3.15 (s, 3H), 3.50 (d, *J* = 8.8 Hz, 1H), 3.59 (s, 3H), 3.78 (s, 3H), 3.89−3.91 (m, 1H), 3.93 (d, *J* = 15.2 Hz, 1H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.47 (d, *J* = 11.6 Hz, 1H), 5.01 (d, *J* = 15.2 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 2H), 7.20−7.31 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 27.0, 32.3, 37.2, 43.3, 55.1, 61.1, 62.3, 70.4, 75.6, 113.9 (2C), 127.5 (2C), 127.7 (2C), 128.1 (2C), 128.3, 129.2, 137.3, 158.9, 172.3, 172.9; HRESIMS calcd for $[C_{24}H_{30}N_2O_5Na]^+$ (M + Na^+) 449.2047, found 449.2046.

(4*R*,5*S*)-1-(4-Methoxybenzyl)-4-benzyloxy-5-[3-oxo-4-(3-(trifluoromethyl)phenyl)butyl]pyrrolidin-2-one (24). To a solution of **23** (120 mg, 0.3 mmol) in THF (12 mL) was added (3-(trifluoromethyl)benzyl)magnesium bromide (1.1 mL, 0.5 M in Et_2O) dropwise at −78 °C with stirring. After being stirred for 45 min, the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL), and the resulting mixture was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/PE 1:1) to give **24** (118 mg, yield: 80%) as a colorless oil: $[\alpha]^{20}_D$ −24.0 (*c* 0.8, $CHCl_3$); IR (film) 3054, 2916, 1720, 1687, 1331, 1265, 1125, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54−1.63 (m, 1H), 1.95−2.03 (m, 1H), 2.38 (t, *J* = 6.8 Hz, 2H), 2.51 (dd, *J* = 2.8, 17.6 Hz, 1H), 2.72 (dd, *J* = 6.8, 17.6 Hz, 1H), 3.43 (dt, *J* = 8.8, 2.8 Hz, 1H), 3.65 (s, 2H), 3.77−3.79 (m, 4H), 3.96 (d, *J* = 15.2 Hz, 1H), 4.32 (d, *J* = 11.6 Hz, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.91 (d, *J* = 15.2 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 7.19−7.53 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 37.07, 37.12, 43.4, 49.1, 55.1, 62.1, 70.5, 75.6, 113.9 (2C), 122.5 (CF_3), 123.9, 125.2 (CF_3), 126.0, 127.6, 127.8 (2C), 128.1 (2C), 128.4 (2C), 129.0, 129.2, 130.7, 131.0, 132.7, 134.5, 137.2, 158.9, 172.1, 205.3; HRESIMS calcd for $[C_{30}H_{30}F_3NO_4Na]^+$ (M + Na^+) 548.2019, found 548.2025.

(4*R*,5*S*,8*R*/*S*)-1-(4-Methoxybenzyl)-4-benzyloxy-5-[3-hydroxy-4-(3-(trifluoromethyl)phenyl)butyl]pyrrolidin-2-one (8*R*)-25a and (8*S*)-25b. To a solution of **24** (110 mg, 0.21 mmol) in anhydrous THF under nitrogen was added (*R*)-2-methyl-CBS-oxazaborolidine (5.8 mg, 0.21 mmol) at −40 °C, and then borane-THF complex (0.32 mL, 0.32 mmol) was slowly added dropwise. After being stirred for 25 h, the reaction was quenched with MeOH (1 mL). The contents of the reaction vessel were poured into EtOAc, and then the combined organic phases were washed with 2 N HCl, a saturated aqueous solution of $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/PE 1:1) to give (8*R*)-**25a** (80 mg, yield: 73%) and (8*S*)-**25b** (27 mg, yield: 24%) as colorless oils: IR (film) 3383, 3020, 2923, 1673, 1513, 1330, 1122, 1073 cm^{-1}; HRESIMS calcd for $[C_{30}H_{32}F_3NO_4Na]^+$ (M + Na^+) 550.2176, found 550.2175.

*(8R)-**25a**.* Data: $[\alpha]^{20}_D$ −17.8 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39−1.46 (m, 2H), 1.54−1.63 (m, 1H), 1.70−1.78 (m, 1H), 2.05 (br s, 1H, D_2O exchangeable), 2.54 (dd, *J* = 2.4, 17.2 Hz, 1H), 2.68 (dd, *J* = 8.4, 13.6 Hz, 1H), 2.76 (dd, *J* = 6.4, 17.2 Hz, 1H), 2.78 (dd, *J* = 4.4, 13.6 Hz, 1H), 3.49 (dt, *J* = 8.8, 2.4 Hz, 1H), 3.72−3.78 (m, 1H), 3.80 (s, 3H), 3.87 (dt, *J* = 6.4, 2.4 Hz, 1H), 3.95 (d, *J* = 15.2 Hz, 1H), 4.38 (d, *J* = 11.6 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.98 (d, *J* = 15.2 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.20−7.54 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 31.8, 37.4, 43.4, 43.9, 55.2, 62.8, 70.6, 71.5, 75.8, 114.1 (2C), 122.9 (CF_3), 123.4, 125.6 (CF_3), 126.0, 127.7 (2C), 127.9 (2C), 128.2 (2C), 128.4 (2C), 128.9, 129.2, 130.6, 130.9, 132.8, 137.5, 139.5, 159.1, 172.6.

*(8S)-**25b**.* Data: $[\alpha]^{20}_D$ −13.9 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32−1.44 (m, 3H), 1.85−1.96 (m, 1H), 2.33 (br s, 1H, D_2O exchangeable), 2.51 (dd, *J* = 2.0, 17.6 Hz, 1H), 2.66 (dd, *J* = 13.6, 8.4 Hz, 1H), 2.70 (dd, *J* = 17.6, 6.4 Hz, 1H), 2.75 (dd, *J* = 13.6, 4.4 Hz, 1H), 3.52- 3.54 (m, 1H), 3.69−3.70 (m, 1H), 3.78 (s, 3H), 3.84−3.86 (m, 1H), 3.98 (d, *J* = 15.2 Hz, 1H), 4.38 (d, *J* = 11.6 Hz, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.90 (d, *J* = 15.2 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 7.20−7.52 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.0, 31.8, 37.4, 43.6, 43.8, 55.2, 63.2, 70.6, 72.0, 75.8, 114.1 (2C), 122.8 (CF_3), 123.4, 125.5 (CF_3), 126.0, 127.7 (2C), 127.9 (2C), 128.3 (2C), 128.4 (2C), 128.9, 129.2, 130.6, 130.9, 132.8, 137.5, 139.4, 159.1, 172.6.

(4*R*,5*S*,8*R*)-1-(4-Methoxybenzyl)-4-benzyloxy-5-[3-benzyloxy-4-(3-(trifluoromethyl)phenyl)butyl]pyrrolidin-2-one (26). To a solution of **25b** (55 mg, 0.104 mmol) with NaH (7.5 mg, 0.31 mmol) and Bu_4NI (10.3 mg, 0.02 mol) in THF (1 mL) was added BnBr (0.04 mL, 0.31 mmol) dropwise at 0 °C with stirring. After being stirred for 18 h at room temperature, the reaction was quenched with H_2O (2 mL), and the resulting mixture was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/PE 1:2) to give **26** (52 mg, yield: 80%) as a colorless oil: $[\alpha]^{20}_D$ −15.3 (*c* 0.8, $CHCl_3$); IR (film) 3030, 2922, 1689, 1330, 1122, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37−1.56 (m, 3H), 1.67−1.75 (m, 1H), 2.54 (dd, *J* = 2.4, 17.6 Hz, 1H), 2.72 (dd, *J* = 6.4, 17.6 Hz, 1H), 2.77 (dd, *J* = 5.2, 13.6 Hz, 1H), 2.91 (dd, *J* = 6.8, 13.6 Hz, 1H), 3.45 (d, *J* = 8.0 Hz, 1H), 3.54−3.60 (m, 1H), 3.79 (s, 3H), 3.81 (dt, *J* = 6.4, 2.4 Hz, 1H), 3.91 (d, *J* = 15.2 Hz, 1H), 4.35 (d, *J* = 11.6 Hz, 1H), 4.37 (d, *J* = 11.6 Hz, 1H), 4.41 (d, *J* = 11.6 Hz, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 4.98 (d, *J* = 15.2 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.21−7.53 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 29.0, 37.4, 40.4, 43.5, 55.2, 62.9, 70.6, 71.8, 75.7, 79.2, 114.1 (2C), 122.9 (CF_3), 123.2, 125.6 (CF_3), 126.1, 127.7 (2C), 127.77 (2C), 127.83 (2C), 127.9 (2C), 128.3 (2C), 128.5 (2C), 128.8, 129.1, 130.5, 130.8, 132.9, 137.5, 138.1, 139.5, 159.0, 172.4; HRESIMS calcd for $[C_{37}H_{38}F_3NO_4Na]^+$ (M + Na^+) 640.2645, found 640.2637.

(4*R*,5*S*,8*R*)-4-Benzyloxy-5-(3-benzyloxy-4-[3-(trifluoromethyl)phenyl)butyl]pyrrolidin-2-one (27). To a solution of **26** (46 mg, 0.07 mmol) in a mixed solvent system ($MeCN/H_2O$ 9:1, v/v, 1.8 mL) was added ceric ammonium nitrate (203 mg, 0.37 mmol) at 0 °C. After being stirred at the same temperature for 2 h, the mixture was allowed to react at room temperature for 4 h. The reaction was quenched with H_2O (2 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/PE 1:1) to give **27** (29 mg, yield: 78%) as a colorless oil: $[\alpha]^{20}_D$ −13.6 (*c* 1.0, $CHCl_3$); IR (film) 3229, 3030, 2924, 1703, 1330, 1123, 1073 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51−1.72 (m, 4H), 2.42 (dd, *J* = 4.0, 17.6 Hz, 1H), 2.63 (dd, *J* = 7.2, 17.6 Hz, 1H), 2.83 (dd, *J* = 5.2, 13.6 Hz, 1H), 2.95 (dd, *J* = 6.8, 13.6 Hz, 1H), 3.57−3.65 (m, 2H), 3.85−3.87 (m, 1H), 4.44 (s, 2H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.53 (d, *J* = 11.6 Hz, 1H), 6.88 (s, 1H), 7.21−7.52 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.0, 30.4, 37.0, 40.4, 60.6, 71.2, 71.6, 79.0, 79.2, 122.9 (CF_3), 123.2, 125.6 (CF_3), 126.2, 127.7 (2C), 127.8 (2C), 127.9 (2C), 128.0 (2C), 128.4, 128.5, 128.8, 130.5, 130.8, 132.9, 137.5, 138.0, 139.6, 175.3; HRESIMS calcd for $[C_{29}H_{30}F_3NO_3Na]^+$ (M + Na^+) 520.2070, found 520.2064.

***iso*-Propyl (4*R*,5*S*,8*R*)-5-(3-(3-benzyloxy-2-(3-benzyloxy-4-(3-(trifluoromethyl)phenyl)butyl)-5-oxopyrrolidin-1-yl)propyl)-thiophene-2-carboxylate (29).** To a mixture of KOH powders (29 mg, 0.52 mmol) and Bu_4NBr (50 mg, 0.16 mol) in THF (5 mL) was added **27** (26 mg, 0.05 mmol) in THF (1 mL), and then a solution of **28** (35 mg, 0.10 mmol) in THF (1 mL) was added dropwise at 0 °C. After being stirred for 4 h at room temperature, the reaction was quenched with a saturated aqueous solution of NH_4Cl (1 mL), and the resulting mixture was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/PE 1:2) to give **29** (22.1 mg, yield: 60%) as a colorless oil: $[\alpha]^{20}_D$ −5.8 (*c* 1.0, $CHCl_3$); IR (film) 3030, 2919, 1702, 1674, 1455, 1264, 1089, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, *J* = 6.0 Hz, 6H), 1.44−1.47 (m, 2H), 1.61−1.68 (m, 2H), 1.80−1.89 (m, 2H), 2.46 (dd, *J* = 2.4, 17.6 Hz, 1H), 2.62 (dd, *J* = 6.4, 17.6 Hz, 1H), 2.82−2.95 (m, 5H), 3.51−3.63 (m, 2H), 3.69−3.76 (m, 1H), 3.79 (dt, *J* = 6.4, 2.4 Hz, 1H), 4.39 (d, *J* = 11.6 Hz, 1H), 4.40 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 5.19 (m, 1H), 6.76 (d, *J* = 4.0 Hz, 1H), 7.19

dx.doi.org/10.1021/jo301277n | J. Org. Chem. XXXX, XXX, XXX−XXX

−7.51 (m, 14H), 7.61 (d, J = 4.0 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9 (2C), 26.5, 27.6, 29.0, 29.2, 37.1, 39.4, 40.4, 63.9, 68.5, 70.7, 71.8, 75.7, 79.1, 122.8 (CF_3), 123.3, 125.5 (CF_3), 125.8, 126.2, 127.6, 127.8 (2C), 127.86 (2C), 127.94 (2C), 128.4 (2C), 128.5, 128.8, 130.6, 130.9, 132.0, 132.8, 133.3, 137.5, 137.9, 139.4, 151.9, 161.8, 172.4; HRESIMS calcd for $[C_{40}H_{44}F_3NO_5SNa]^+$ (M + Na$^+$) 730.2784, found 730.2793.

***iso*-Propyl (4*R*,5*S*,8*R*)-5-(3-(3-hydroxy-2-(3-hydroxy-4-(3-(trifluoromethyl)phenyl)butyl)-5-oxopyrrolidin-1-yl)propyl)-thiophene-2-carboxylate (30).** To a solution of **29** (12 mg, 0.017 mmol) in CH_2Cl_2 (0.1 mL) was added BBr_3 (0.5 M, 0.068 mL, 0.034 mmol) at −10 °C. After being stirred for 40 min, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$, and the resulting mixture was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc) to give **30** (6 mg, yield: 70%) as a colorless oil: $[\alpha]^{20}_D$ −5.6 (c 0.6, $CHCl_3$); IR (film) 3390, 2928, 1702, 1687, 1460, 1330, 1284, 1091, 799, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (d, J = 6.5 Hz, 6H), 1.52−1.58 (m, 3H), 1.75 −1.97 (m, 4H), 2.07 (br s, 1H, D_2O exchangeable), 2.31 (d, J = 17.0 Hz, 1H), 2.69−2.96 (m, 6H), 3.48 (d, J = 8.0 Hz, 1H), 3.67−3.73 (m, 1H), 3.86−3.89 (m, 1H), 4.16−4.17 (m, 1H), 5.15 (m, 1H), 6.79 (d, J = 4.0 Hz, 1H), 7.38−7.44 (m, 2H), 7.46 (s, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.57 (d, J = 4.0 Hz, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9 (2C), 26.9, 27.7, 29.0, 32.0, 39.5, 40.2, 44.0, 66.5, 68.6, 69.4, 71.9, 123.0 (CF_3), 123.6, 125.2 (CF_3), 125.6, 126.0, 129.1, 130.7, 131.0, 132.1, 132.8, 133.3, 139.1, 152.0, 161.9, 172.4; HRESIMS calcd for $[C_{26}H_{32}F_3NO_5SNa]^+$ (M + Na$^+$) 550.1845, found 550.1848.

(4*R*,5*S*,8*R*)-5-(3-(3-Hydroxy-2-(3-hydroxy-4-(3-(trifluoromethyl)phenyl)butyl)-5-oxopyrrolidin-1-yl)propyl)-thiophene-2-carboxylic acid (31). To a solution of **30** (11 mg, 0.021 mmol) in the mixture of MeOH/THF/H_2O (2.5 mL, 3:3:1) was added LiOH·H_2O (7.8 mg, 0.19 mmol) at 0 °C. After being stirred for 3 days at room temperature, the reaction was concentrated in vacuo. The residue was dissolved in water (2 mL) and then neutralized by an aqueous solution of HCl (2 N) until pH = 2, and the resulting mixture was extracted with EtOAc (3 × 4 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: MeOH/CH_2Cl_2 1:10) to give **31** (9.7 mg, yield: 95%) as a white waxy solid: $[\alpha]^{20}_D$ +7.1 (c 0.9, MeOH); IR (film) 3357, 2932, 1736, 1665, 1331, 1122, 1074 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.42−1.60 (m, 3H), 1.74−1.77 (m, 1H), 1.88−1.97 (m, 2H), 2.22 (dd, J = 1.5, 17.5 Hz, 1H), 2.74 (dd, J = 6.0, 17.5 Hz, 1H), 2.77−2.90 (m, 4H), 3.00−3.02 (m, 1H), 3.49−3.50 (m, 1H), 3.63−3.68 (m, 1H), 3.80−3.85 (m, 1H), 4.12−4.14 (m, 1H), 6.85 (d, J = 3.5 Hz, 1H), 7.45−7.52 (m, 4H), 7.55 (s, J = 3.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 27.5, 28.4, 30.1, 33.2, 40.7, 40.8, 44.6, 68.7, 69.5, 72.7, 123.9 (CF_3), 124.7, 126.5 (CF_3), 126.9, 127.1, 130.0, 131.3, 131.6, 132.4, 133.2, 134.4, 141.8, 152.3, 168.4, 175.5; $[C_{23}H_{25}F_3NO_5S]^-$ (M − H$^+$) 484.1411, found 484.1394.

Methyl (4*R*,5*S*,8*R*)-7-(3-benzyloxy-2-(3-benzyloxy-4-(3-(trifluoromethyl)phenyl)butyl)-5-oxopyrrolidin-1-yl)-heptanoate (33). To a mixture of KOH powders (82 mg, 1.5 mmol) and Bu_4NBr (142 mg, 0.44 mol) in THF (5 mL) was added **27** (73 mg, 0.15 mmol) in THF (7 mL), and then a solution of **32** (79 mg, 0.29 mmol) in THF (2 mL) was added dropwise at 0 °C. After being stirred for 4 h at room temperature, the reaction was quenched with a saturated aqueous solution of NH_4Cl (1 mL), and the resulting mixture was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/PE 1:2) to give **33** (58 mg, yield: 60%) as a colorless oil: $[\alpha]^{20}_D$ −6.0 (c 0.7, $CHCl_3$); IR (film) 3031, 2928, 1736, 1688, 1330, 1122, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26−1.37 (m, 4H), 1.44−1.52 (m, 5H), 1.58−1.70 (m, 3H), 2.30 (t, J = 7.6 Hz, 2H), 2.45 (dd, J = 2.4, 17.6 Hz, 1H), 2.61 (dd, J = 6.4, 17.6 Hz, 1H), 2.75−2.83 (m, 2H), 2.96 (dd, J = 6.4, 13.6 Hz, 1H), 3.52−3.54 (m, 1H), 3.61−3.66 (m, 1H), 3.66−3.70 (m, 1H), 3.67 (s, 3H), 3.78 (dt, J = 6.4, 2.4 Hz, 1H), 4.40 (d, J = 12.0 Hz, 1H), 4.41 (d, J = 11.6 Hz, 1H), 4.46 (d, J = 11.6 Hz, 1H), 4.51 (d, J = 12.0 Hz, 1H), 7.20−7.53 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 26.3, 26.4, 26.9, 28.7, 29.1, 33.9, 37.1, 39.9, 40.4, 51.4, 63.6, 70.7, 71.7, 75.6, 79.2, 122.8 (CF_3), 123.2, 125.5 (CF_3), 126.1, 127.6 (2C), 127.7 (2C), 127.8 (2C), 127.9 (2C), 128.39 (2C), 128.45, 128.8, 130.5, 130.8, 137.5, 137.9, 139.4, 172.0, 174.1; HRESIMS calcd for $[C_{37}H_{44}F_3NO_5Na]^+$ (M + Na$^+$) 662.3064, found 662.3069.

Methyl (4*R*,5*S*,8*R*)-7-(3-hydroxy-2-(3-hydroxy-4-(3-(trifluoromethyl)phenyl)butyl)-5-oxopyrrolidin-1-yl)-heptanoate (34). To a solution of **33** (54 mg, 0.08 mmol) in methanol (3 mL) was added Pd/C 10% (54 mg). After the reaction flask was purged with hydrogen, the reaction mixture was stirred for 24 h at room temperature. The mixture was then filtered through Celite, and the filtrate was concentrated under reduced pressure to give **34** (35 mg, yield: 90%) as a colorless oil: $[\alpha]^{20}_D$ −6.8 (c 1.0, $CHCl_3$); IR (film) 3380, 2919, 1725, 1674, 1122, 700 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 1.29−1.35 (m, 5H), 1.51−1.62 (m, 6H), 1.71−1.81 (m, 1H), 2.20 (dd, J = 1.6, 17.6 Hz, 1H), 2.31 (t, J = 7.2 Hz, 2H), 2.72 (dd, J = 6.4, 17.6 Hz, 1H), 2.77−2.97 (m, 3H), 3.46 (d, J = 6.4 Hz, 1H), 3.55−3.60 (m, 1H), 3.64 (s, 3H), 3.80−3.86 (m, 1H), 4.11 (d, J = 6.4 Hz, 1H), 7.47−7.52 (m, 3H), 7.56 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 25.8, 27.3, 27.4, 27.9, 29.7, 33.1, 34.7, 40.8, 41.2, 44.6, 51.9, 68.4, 69.5, 72.7, 123.9 (CF_3), 124.5, 127.1 (CF_3), 129.85, 129.96, 131.3, 131.6, 134.4, 141.8, 175.2, 175.9; HRESIMS calcd for $[C_{23}H_{32}F_3NO_5Na]^+$ (M + Na$^+$) 482.2125, found 482.2131.

(4*R*,5*S*,8*R*)-7-(3-Hydroxy-2-(3-hydroxy-4-(3-(trifluoromethyl)phenyl)butyl)-5-oxopyrrolidin-1-yl)heptanoic acid (35). To a solution of **34** (30 mg, 0.065 mmol) in the mixture of MeOH/THF/H_2O (2.5 mL, 3:3:1) was added LiOH·H_2O (8.2 mg, 0.195 mmol) at 0 °C. After being stirred for 24 h at room temperature, the reaction mixture was concentrated in vacuo. The residue was dissolved in water (2 mL) and then neutralized by an aqueous solution of HCl (2 N) until pH = 2, and the resulting mixture was extracted with EtOAc (3 × 4 mL). The combined organic phases were then dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: MeOH/CH_2Cl_2 1:10) to give **38** (28 mg, yield: 95%) as a white waxy solid: $[\alpha]^{20}_D$ +10.6 (c 1.0, MeOH); IR (film) 3359, 2931, 1661, 1330, 1121, 1074 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 1.29−1.40 (m, 5H), 1.44−1.62 (m, 6H), 1.76−1.80 (m, 1H), 2.21 (dd, J = 2.0, 17.5 Hz, 1H), 2.25 (t, J = 7.5 Hz, 2H), 2.72 (dd, J = 6.5, 17.5 Hz, 1H), 2.80 (dd, J = 7.5, 14.0 Hz, 1H), 2.87 (dd, J = 5.0, 14.0 Hz, 1H), 2.91−2.97 (m, 1H), 3.47 (d, J = 6.5 Hz, 1H), 3.56−3.62 (m, 1H), 3.81−3.86 (m, 1H), 4.11 (d, J = 6.5 Hz, 1H), 7.46−7.52 (m, 3H), 7.56 (s, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 26.3, 27.38, 27.44, 27.9, 29.8, 33.1, 35.9, 40.8, 41.2, 44.6, 68.5, 69.5, 72.7, 123.9 (CF_3), 124.7, 126.9 (CF_3), 127.1, 130.0, 131.4, 131.6, 134.4, 141.8, 175.2, 179.5; HRESIMS calcd for $[C_{22}H_{29}F_3NO_5]^-$ (M − H$^+$) 444.2003, found 444.1989.

(4*R*,5*S*,8*R*)-1-(4-Methoxybenzyl)-4-hydroxy-5-[3-hydroxy-4-(3-(trifluoromethyl)phenyl)butyl]pyrrolidin-2-one (36). To a solution of (8*R*)-**25a** (14 mg, 0.027 mmol) in methanol (3 mL) was added Pd/C 10% (13 mg). After the reaction flask was purged with hydrogen, the reaction mixture was stirred for 24 h at room temperature. The mixture was then filtered through Celite, and the filtrate was concentrated under reduced pressure to give **36** (11 mg, yield: 90%) as a colorless oil: $[\alpha]^{20}_D$ −15.6 (c 1.1, $CHCl_3$); IR (film) 3417, 2919, 2353, 1666, 1331, 1247, 1121 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36−1.56 (m, 3H), 1.84−1.93 (m, 1H), 2.36 (dd, J = 2.4, 17.6 Hz, 1H), 2.65 (dd, J = 8.6, 13.6 Hz, 1H), 2.76 (dd, J = 6.7, 17.6 Hz, 1H), 2.78 (dd, J = 4.4, 13.6 Hz, 1H), 3.37−3.39 (m, 1H), 3.67−3.71 (m, 1H), 3.76 (s, 3H), 3.98 (d, J = 15.0 Hz, 1H), 4.13−4.15 (m, 1H), 4.84 (d, J = 15.0 Hz, 1H), 6.83 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 7.8 Hz, 1H), 7.40−7.44 (m, 2H), 7.50 (d, J = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2, 31.6, 40.1, 43.7, 43.9, 55.2, 66.0, 69.1, 72.3, 114.1 (2C), 122.7 (CF_3), 123.5, 125.4 (CF_3), 125.9, 128.3 (2C), 129.0, 129.3, 130.8, 131.1, 132.8, 139.1, 159.1, 172.6; HRESIMS calcd for $[C_{23}H_{26}F_3NO_4Na]^+$ (M + Na$^+$) 460.1700, found 460.1709.

Mosher Esters of (8*S*)-25b: Compounds 37a and 37b. A solution of (*S*)-(−)-MTPA (7.9 mg, 0.034 mmol) in 1 mL of DCM was cooled to 0 °C for 10 min. To this solution was successively added (8*S*)-**25b** (15.0 mg, 0.028 mmol) followed by EDCI (10.7 mg, 0.056 mmol) and DMAP (1.0 mg, 0.008 mmol). The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by a saturated aqueous solution of NH_4Cl (1 mL), and the resulting mixture was extracted with diethyl ether (3 × 5 mL). The combined organic phases were washed with brine (1 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: hexanes/ethyl acetate 1:2) to afford compound **37a** (7 mg, yield: 34%) as a colorless oil: $[\alpha]^{20}_D$ −21.0 (*c* 1.1, $CHCl_3$); IR (film) 2918, 2849, 1744, 1690, 1330,1166, 702 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.21 (m, 1H), 1.47 (m, 2H), 1.61 (m, 1H), 2.47 (dd, *J* = 2.4, 17.4 Hz, 1H), 2.61 (dd, *J* = 6.6, 17.4 Hz, 1H), 2.83 (dd, *J* = 6.0, 14.4 Hz, 1H), 2.91 (dd, *J* = 7.8, 14.4 Hz, 1H), 3.33 (dt, *J* = 8.4, 2.4 Hz, 1H), 3.36 (s, 3H), 3.66 (dt, *J* = 6.6, 2.4 Hz, 1H), 3.75 (d, *J* = 15.0 Hz, 1H), 3.77 (s, 3H), 4.31 (d, *J* = 11.4 Hz, 1H), 4.39 (d, *J* = 11.4 Hz, 1H), 4.86 (d, *J* = 15.0 Hz, 1H), 5.24 (m, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 6.6 Hz, 2H), 7.19−7.41 (m, 11H), 7.52 (d, *J* = 7.8 Hz, 1H); MS (ESI, *m*/*z*) 744 (M + H$^+$); HRESIMS calcd for $[C_{40}H_{39}F_6NO_6Na]^+$ (M + Na$^+$) 766.2574, found 766.2577.

Following the same procedure, the esterification of (8*S*)-**25b** with (*R*)-(+)-MTPA afforded **37b** in 20% yield as a colorless oil: $[\alpha]^{20}_D$ −15.6 (*c* 0.4, $CHCl_3$); IR (film) 2918, 2849, 1744, 1690, 1330,1166, 702 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.33 (m, 1H), 1.50 (m, 2H), 1.70 (m, 1H), 2.50 (dd, *J* = 2.4, 17.4 Hz, 1H), 2.65 (dd, *J* = 6.6, 17.4 Hz, 1H), 2.79 (dd, *J* = 5.4, 14.4 Hz, 1H), 2.87 (dd, *J* = 7.8, 14.4 Hz, 1H), 3.32 (s, 3H), 3.40 (dt, *J* = 8.4, 2.4 Hz, 1H), 3.72 (dt, *J* = 6.6, 2.4 Hz, 1H), 3.77 (s, 3H), 3.85 (d, *J* = 15.0 Hz, 1H), 4.33 (d, *J* = 12.0 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.88 (d, *J* = 15.0 Hz, 1H), 5.20 (m, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.19−7.38 (m, 13H), 7.47 (d, *J* = 7.8 Hz, 1H); MS (ESI, *m*/*z*) 744 (M + H$^+$); HRESIMS calcd for $[C_{40}H_{39}F_6NO_6Na]^+$ (M + Na$^+$) 766.2574, found 766.2577.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of all new compounds and crystal data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Fax: 86-592-2186400. E-mail: pqhuang@xmu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful to National Basic Research Program (973 Program) of China (Grant No. 2010CB833200) and the NSF of China (21072160; 20832005) for financial support.

■ REFERENCES

(1) Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533−1564.

(2) Das, S.; Chandrasekhar, S.; Yadav, J. S.; Grée, R. *Chem. Rev.* **2007**, *107*, 3286−3337.

(3) Smith, R. L.; Lee, T.-J.; Gould, N. P.; Cragoe, E. J., Jr.; Oien, H. G.; Kuehl, F. A., Jr. *J. Med. Chem.* **1977**, *20*, 1292−1299.

(4) (a) Billot, X.; Chateauneuf, A.; Chauret, N.; Denis, D.; Greig, G.; Mathieu, M.-C.; Metters, K. M.; Slipetz, D. M.; Young, R. N. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1129−1132. (b) Young, R. N.; Billot, X.; Han, Y.; Slipetz, D. A.; Chauret, N.; Belley, M.; Metters, K.; Mathieu, M.-C.; Greig, G. M.; Denis, D.; Girard, M. *Heterocycles* **2004**, *64*, 437−446.

(5) Cameron, K. O.; Lefker, B. A.; Chu-Moyer, M. Y.; Crawford, D. T.; Jardine, P. D.; DeNinno, S. L.; Gilbert, S.; Grasser, W. A.; Ke, H.; Lu, B.; Owen, T. A.; Paralkar, V. M.; Qi, H.; Scott, D. O.; Thompson, D. D.; Tjoa, C. M.; Zawistoski, M. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1799−1802.

(6) Bates, R. W.; Sridhar, S. *Synlett* **2009**, 1979−1981.

(7) (a) Elworthy, T. R.; Kertesz, D. J.; Kim, W.; Roepel, M. G.; Quattrocchio-Setti, L.; Smith, D. B.; Tracy, J. L.; Chow, A.; Li, F.; Brill, E. R.; Lach, L. K.; Mcgee, D.; Yang, D. S.; Chiou, S.-S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1655−1659. (b) Elworthy, T. R.; Brill, E. R.; Chiou, S.-S.; Chu, F.; Harris, J. R.; Hendricks, R. T.; Huang, J.; Kim, W.; Lach, L. K.; Mirzadegan, T.; Yee, C.; Walker, K. A. M. *J. Med. Chem.* **2004**, *47*, 6124−6127. (c) Elworthy, T. R.; Brill, E. R.; Caires, C. C.; Kim, W.; Lach, L. K.; Tracy, J. L.; Chiou, S.-S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2523−2526. (d) Xiao, Y.; Araldi, G.; Zhao, Z.; Brugger, N.; Karra, S.; Fischer, D.; Palmer, E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4323−4327. (e) Nair, S. K.; Matthews, J. J.; Cripps, S. J.; Ma, C.-R.; Dovalsantos, E. Z.; Grubbs, A. W.; Sach, N. W.; Hoeve, W. T.; Koster, H.; Flahive, E. J.; Tanis, S. P.; Renner, M.; Wiltenburg, J. V. *Tetrahedron Lett.* **2010**, *51*, 1451−1454.

(8) For a review involving the generation and application of α-lithioamines, see: (a) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069−1084. For selected examples, see: (b) Dieter, R. K.; Lu, K. *J. Org. Chem.* **2002**, *67*, 847−855. (c) Bilke, J. L.; Moore, S. P.; O'Brien, P.; Gilday, J. *Org. Lett.* **2009**, *11*, 1935−1938.

(9) (a) Zheng, X.; Feng, C.-G.; Ye, J.-L.; Huang, P.-Q. *Org. Lett.* **2005**, *7*, 553−556. (b) Zheng, X.; Zhu, W.-F.; Huang, P.-Q. *Sci. China: Chem.* **2010**, *53*, 1914−1920.

(10) (a) Haeffner, F.; Brandt, P.; Gawley, R. E. *Org. Lett.* **2002**, *4*, 2101−2104. (b) Iula, D. M.; Gawley, R. E. *J. Org. Chem.* **2000**, *65*, 6196−6201.

(11) Huang, P.-Q.; Zheng, X.; Wang, S.-L.; Ye, J.-L.; Jin, L.-R.; Chen, Z. *Tetrahedron: Asymmetry* **1999**, *10*, 3309−3317.

(12) For β-elimination during the 1C-lithiation of sugars, see: (a) Lancelin, J. M.; Luc, M. A.; Sinay, P. *Chem. Commun.* **1984**, *6*, 355−356. (b) Schmidt, R. R.; Kast, J. *Tetrahedron Lett.* **1986**, *27*, 4007−4010. (c) Pedretti, V.; Veyrières, A.; Sinaÿ, P. *Tetrahedron* **1990**, *46*, 77−88. (d) Mazéas, D.; Skrydstrup, D. T.; Beau, J. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 909−912.

(13) (a) Hart, D. J.; Tsai, Y. M. *J. Am. Chem. Soc.* **1982**, *104*, 1430−1432. (b) Hart, D. J.; Kanai, K. *J. Am. Chem. Soc.* **1983**, *105*, 1255−1263. (c) Burnett, D. A.; Choi, J. K.; Hart, D. J.; Tsai, Y. M. *J. Am. Chem. Soc.* **1984**, *106*, 8201−8209. (d) Hart, D. J.; Tsai., Y. M. *J. Am. Chem. Soc.* **1984**, *106*, 8209−8217. (e) Dener, J. M.; Hart, D. J.; Ramesh, S. *J. Org. Chem.* **1988**, *53*, 6022−6030. (f) Choi, J. K.; Ha, D. C.; Hart, D. J.; Lee, C. S.; Ramesh, S.; Wu, S. *J. Org. Chem.* **1989**, *54*, 279−290. For applications of this methodology, see: (g) Tsai, Y. M.; Nieh, H. C.; Pan, J. S.; Hsiao, D. D. *Chem. Commun.* **1996**, 2469−2470. (h) Clauss, R.; Hunter, R. *J. Chem. Soc., Perkin Trans. 1* **1997**, 71−76. (i) Hunter, R.; Richards, P. *Tetrahedron Lett.* **2000**, *41*, 3755−3758. (j) Hunter, R.; Richards, P. *Org. Biomol. Chem.* **2003**, *1*, 2348−2356. (k) Khim, S. K.; Schultz, A. G. *J. Org. Chem.* **2004**, *69*, 7734−7736. (l) Bogliotti, N.; Dalko, P. I.; Cossy, J. *Synlett* **2005**, 349−351.

(14) For related reviews, see: (a) Renaud, P.; Giraud, L. *Synthesis* **1996**, 913−926. (b) Hart, D. J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 279−302. (c) Aurrecoechea, J. M.; Suero, R. *Arkivoc* **2004**, part (xiv), 10−35 at www.arkat-usa.org.

(15) (a) Chen, M.-J.; Tsai, Y. M. *Tetrahedron* **2011**, *67*, 1564−1574. (b) Chen, M.-J.; Tsai, Y. M. *Tetrahedron Lett.* **2007**, *48*, 6271−6274.

(16) For selected reviews on the chemistry of SmI_2, see: (a) Procter, D. J.; Flowers, R. A., Skrydstrup, T., Eds.; *Organic Synthesis using Samarium Diiodide: A Practical Guide*; Royal Society of Chemistry Publishing: London, 2010. (b) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7140−7165. (c) Lin, G.-Q.; Xu, M.-H.; Zhong, Y.-W.; Sun, X.-W. *Acc. Chem. Res.* **2008**, *41*, 831−840. (d) Gopalaiah, K.; Kagan, H. B. *New J. Chem.* **2008**, *32*, 607−637. (e) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351−10372. (f) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371−3403. (g) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745−777. (h) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338.

(17) (a) Liu, X.-K.; Zheng, X.; Ruan, Y.-P.; Ma, J.; Huang, P.-Q. *Org. Biom. Chem.* **2012**, *10*, 1275−1284. (b) Liu, X.-K.; Qiu, S.; Xiang, Y.-G.; Ruan, Y.-P.; Zheng, X.; Huang, P.-Q. *J. Org. Chem.* **2011**, *76*, 4952−4963. (c) Lin, G.-J.; Zheng, X.; Huang, P.-Q. *Chem. Commun.* **2011**, *47*,

1545−1547. (d) Wu, S.-F.; Ruan, Y.-P.; Zheng, X.; Huang, P.-Q. *Tetrahedron* **2010**, *66*, 1653−1660. (e) Xiang, Y.-G.; Wang, X.-W.; Zheng, X.; Ruan, Y.-P.; Huang, P.-Q. *Chem. Commun.* **2009**, 7045−7047. (f) Wu, S.-F.; Zheng, X.; Ruan, Y.-P.; Huang, P.-Q. *Org. Biomol. Chem.* **2009**, *7*, 2967−2975.

(18) Chai, Y.-F.; Guo, C.; Jiang, K.-Z.; Pan, Y.-J.; Sun, C. *Org. Biomol. Chem.* **2012**, *10*, 791−797.

(19) (a) Mazéas, D.; Skrydstrup, T.; Beau, J.-M. *Angew. Chem., Int. Ed.* **1995**, *34*, 909−912. (b) Skrydstrup, T.; Jarreton, O.; Mazeas, D.; Urban, D.; Beau, J.-M. *Chem.—Eur. J.* **1998**, *4*, 655−671. (c) Urban, D.; Skrydstrup, T.; Beau, J.-M. *J. Org. Chem.* **1998**, *63*, 2507−2516. (d) Doisneau, G.; Beau, J.-M. *Tetrahedron Lett.* **1998**, *39*, 3477−3480. (e) Miquel, N.; Doisneau, G.; Beau, J.-M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4111−4114.

(20) (a) Huang, P.-Q.; Xu, T.; Chen, A.-Q. *Synth. Commun.* **2000**, *30*, 2259−2268. (b) Huang, P.-Q.; Fei, X.-S.; Ruan, Y.-P.; Zhuang, A.-C.; Chen, Z.-Y. *J. Xiamen Univ., Nat. Sci.* **1996**, *35*, 913−917.

(21) Satsuki, I.; Hiroaki, S.; Takuji, H.; Hiroyuki, N. *Enantiomer* **1998**, *3*, 187−189.

(22) (a) Bernardi, A.; Micheli, F.; Potenza, D.; Scolastico, C.; Villa, R. *Tetrahedron Lett.* **1990**, *31*, 4949−4952. (b) Huang, P.-Q.; Wang, S.-L.; Ye, J.-L.; Ruan, Y.-P.; Huang, Y.-Q.; Zheng, H.; Gao, J.-X. *Tetrahedron* **1998**, *54*, 12547−12560.

(23) Curren, D. P. B. *Stereochemitry of Radical Reactions*; VCH Publishers, Inc.: Weinheim, 1996.

(24) Huang, P.-Q.; Chen, Q.-F.; Chen, C.-L.; Zhang, H.-Q. *Tetrahedron: Asymmetry* **1999**, *10*, 3827−3832.

(25) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818.

(26) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553.

(27) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

(28) Lucet, D.; Heyse, P.; Gissot, A.; Gall, T. L.; Mioskowski, C. *Eur. J. Org. Chem.* **2000**, 3575−3579.

(29) For selected examples on the SmI_2-medaited intermolecular coupling reactions, see: nitrones with activated alkenes: (a) Masson, G.; Cividino, P.; Py, S.; Vallée, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 2265−2268. (b) Riber, D.; Skrydstrup, T. *Org. Lett.* **2003**, *5*, 229−231. (c) Masson, G.; Zeghida, W.; Cividino, P.; Py, S.; Vallée, Y. *Synlett* **2003**, 1527−1529. (d) Johannesen, S. A.; Albu, S.; Hazell, R. G.; Skrydstrup, T. *Chem. Commun.* **2004**, 1962−1963. (e) Desvergnes, S.; Py, S.; Vallée, Y. *J. Org. Chem.* **2005**, *70*, 1459−1462. (f) Cividino, P.; Py, S.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2007**, *72*, 485−493. (g) Rehák, J.; Fišera, L.; Podolan, G.; Kožíšek, J.; Perašínová, L. *Synlett* **2008**, 1260−1264. (h) Rehak, J.; Fisera, L.; Kozisek, J.; Bellovicova, L. *Tetrahedron* **2011**, *67*, 5762−5769. (i) Gilles, P.; Py, S. *Org. Lett.* **2012**, *14*, 1042−1045. Nitrones with aldehydes: (j) Burchak, O. N.; Masson, G.; Py, S. *Synlett* **2010**, 1623−1626. Aldehydes with activated alkenes: (k) Vogel, J. C.; Butler, R.; Procter, D. J. *Tetrahedron* **2008**, *64*, 11876−11883. (l) Xu, M.-H.; Wang, W.; Lin, G.-Q. *Org. Lett.* **2000**, *2*, 2229−2232. Nitrones with *N*-*tert*-butanesulfinyl imines: (m) Zhong, Y.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, *6*, 3953−3956. *N*-*tert*-Butanesulfinyl imines with aldehydes: (n) Zhong, Y.-W.; Dong, Y.-Z.; Fang, K.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 11956−11957.

(30) (a) Song, X.-N.; Yao, Z. J. *Tetrahedron* **2010**, *66*, 2589−2593. (b) Jin, S.; Li, C.; Ma, Y.; Kan, Y.; Zhang, Y.-J.; Zhang, W. *Org. Biomol. Chem.* **2010**, *8*, 4011−4015. (c) Ma, Y.; Jin, S.; Kan, Y.; Zhang, Y.-J.; Zhang, W. *Tetrahedron* **2010**, *66*, 3849−3854. (d) Ma, Y.; Zhang, Y.-J.; Jin, S.; Li, Q.; Li, C.; Lee, J.; Zhang, W. *Tetrahedron Lett.* **2009**, *50*, 7388−7391. (e) Ekaterina, S.; Jacob, K.; Israel, G.; M, K. *Chem. Commun.* **2009**, 3053−3055. (f) Sulzer, M. S.; Alexakis, A.; Mareda, J.; Bollot, G.; Bernardinelli, G.; Filinchuk, Y. *Chem.—Eur. J.* **2009**, *15*, 3204−3220. (g) Suzuki, K.; Oldenburg, P. D.; Que, L., Jr. *Angew. Chem., Int. Ed.* **2008**, *47*, 1887−1889. (h) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783−787. (i) Sarah, S. M.; Alexandre, A. *Chem. Commun.* **2007**, 3123−3135. (j) Denmark, S. E.; Fu, J.; Lawler, M. J. *J. Org. Chem.* **2006**, *71*, 1523−1536. (k) Alexakis, A; Andrey, O. *Org. Lett.* **2002**, *4*, 3611−3614. (l) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488−9489. (m) Tohru, O.; Masahiro, H. *J. Org. Chem.* **1989**, *54*, 5834−5835.