Total Synthesis of (±)-Lepadiformine A via Radical Translocation–Cyclization Reaction

Manabu Fujitani, Masami Tsuchiya, Kentaro Okano, Kiyosei Takasu,[1] Masataka Ihara,[2] Hidetoshi Tokuyama*

Graduate School of Pharmaceutical Sciences, Tohoku University, Aramaki, Aoba-ku, 980-8578 Sendai, Japan
Fax +81(22)7956877; E-mail: tokuyama@mail.pharm.tohoku.ac.jp

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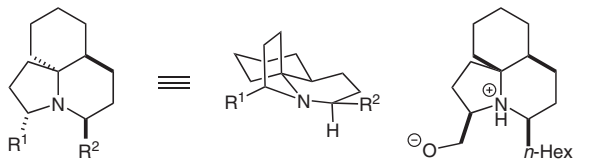
Abstract: A total synthesis of (±)-lepadiformine A was accomplished through construction of the 1-azaspiro[4.5]decane skeleton by a sequential radical translocation–cyclization reaction.

Key words: radical reaction, cyclization, domino reaction, natural products, total synthesis

A variety of structurally unique alkaloids are found in marine sources. Among them, lepadiformines (A–C, **1**–**3**) isolated from the tunicate *Clavelina lepadiformis* and *Clavelina moluccensis* by Biard and co-workers (Figure 1),[3] exhibit modest cytotoxic activity towards various cardiovascular effects in vitro and in vivo.[3b,4] In 2000, Kibayashi and co-workers revised the originally proposed structure of lepadiformine (**4**) to structure **1** by their first total synthesis.[5a] Because of the unique azaspirocyclic skeleton with four asymmetric stereocenters, these compounds have been attractive targets for the synthetic community. To date, a number of synthetic approaches have been reported.[5]

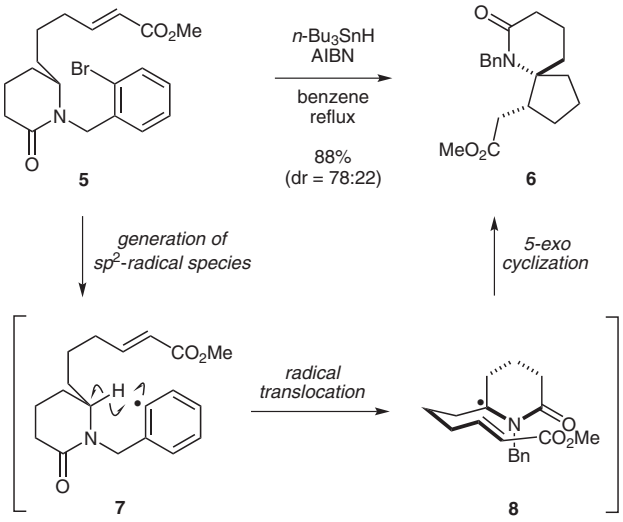


lepadiformine A (**1**) $R^1 = CH_2OH$, R^2 = *n*-Hex
B (**2**) $R^1 = CH_2OH$, R^2 = *n*-Bu
C (**3**) R^1 = H, R^2 = *n*-Bu

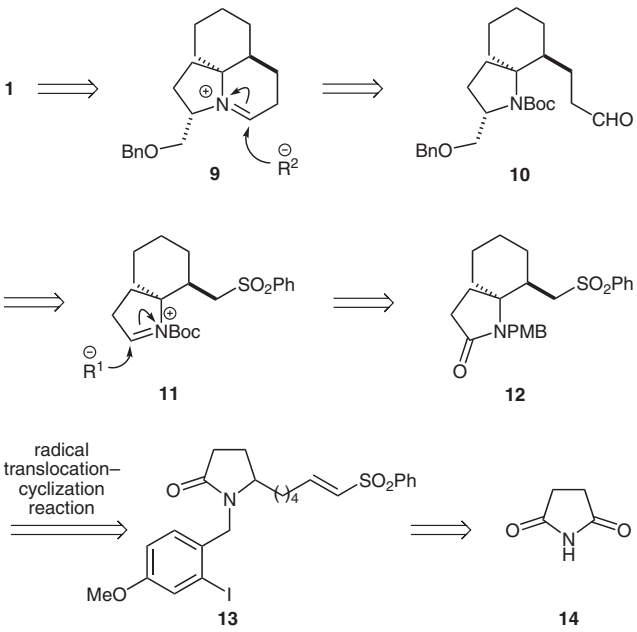
putative lepadiformine (**4**)

Figure 1 The family of lepadiformines A–C (**1**–**3**) and the putative structure of lepadiformine (**4**)

Recently, we have developed a diastereoselective cascade radical translocation–cyclization reaction[6] to construct the 6-azaspiro[4.5]decane skeleton of (±)-halichlorine (Scheme 1).[7] The reaction is initiated by the 1,5-radical translocation from sp^2-radical **7** to generate the more stable nitrogen-substituted sp^3-radical **8**. Then 5-*exo* cyclization proceeds to construct the azaspiro compound **6**. This reaction was proven to be quite effective for stereoselective construction of the consecutive quaternary and tertiary stereogenic centers from a readily available lactam precursor under neutral conditions. During the studies of this process, we then investigated the feasibility of the construction of a 1-azaspiro[4.5]decane framework, which is the core skeleton of lepadiformines. Herein, we report the total synthesis of (±)-lepadiformine A (**1**) fea-



Scheme 1 Stereoselective construction of 6-azaspiro[4.5]decane skeleton of (±)-halichlorine



Scheme 2 Retrosynthetic analysis

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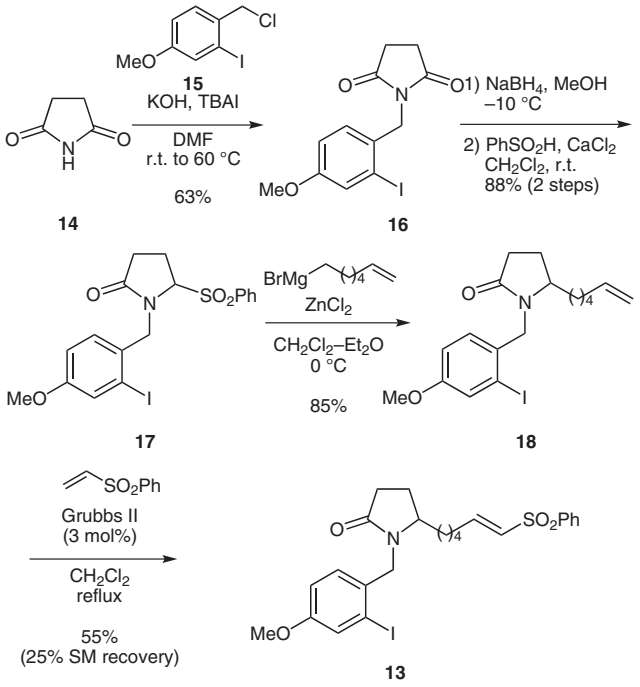


Scheme 3 Synthesis of the precursor for the radical translocation–cyclization reaction

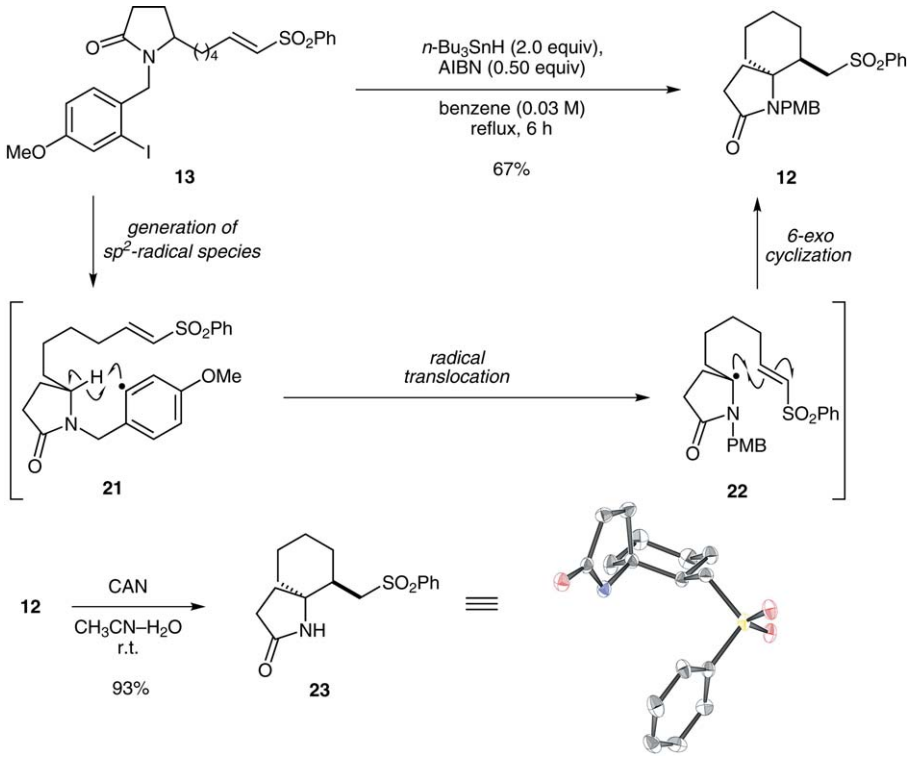
turing a diastereoselective radical translocation–cyclization reaction.

We planned to introduce two alkyl chains (R^1 and R^2) at the later stage of the synthesis, which would provide facile access to a variety of derivatives (Scheme 2). According to several synthetic studies,[5b,d,m] lepadiformine A (**1**) is derived from aldehyde **10** via diastereoselective nucleophilic addition to the iminium ion **9**. Compound **10** could be prepared from lactam **12** by introduction of a hydroxymethyl group followed by alkylation at the α-position of sulfone.

For the crucial construction of the azaspirocyclic framework, we applied the radical translocation–cyclization reaction to alkenyl sulfone **13**, which is readily prepared from succinimide (**14**).

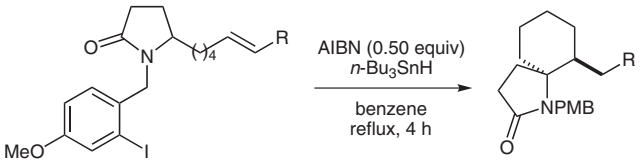
The synthesis of the precursor for the key radical reaction commenced with alkylation of succinimide (**14**) with known benzyl chloride **15** according to the reported procedure (Scheme 3).[8] The imide **16** thus obtained was transformed to the corresponding sulfone **17** by partial reduction of imide and subsequent sulfonylation. The alkyl side chain was then introduced by addition of a Grignard reagent in the presence of $ZnCl_2$ to provide **18**,[9] which was subjected to cross metathesis with vinyl sulfone to give the radical reaction precursor **13**.[10]

We were delighted to find that the key radical translocation–cyclization reaction took place smoothly to furnish the desired azaspirocyclic compound **12** in good yield as a single diastereomer (Table 1). Among reaction conditions tested, combination of AIBN (0.50 equiv) and *n*-Bu_3SnH (2.0 equiv) was found to effective to reduce the amount of deiodinated **13** and give the desired **12** in 60% yield with excellent diastereoselectivity (entries 1 and 2).[11,12] The radical reaction also proceeded with a substrate **19** comprising an α,β-unsaturated ester moiety to provide the corresponding azaspirocyclic compound **20** in a moderate yield (entry 3). Deprotection of the PMB group[13] provided crystalline lactam **23**, which allowed us



Scheme 4 Radical translocation–cyclization reaction and determination of the relative stereochemistry by X-ray crystallography

Table 1 Radical Translocation–Cyclization Reaction

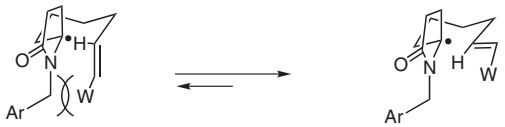


13 R = SO_2Ph
19 R = CO_2Me

12 R = SO_2Ph
20 R = CO_2Me

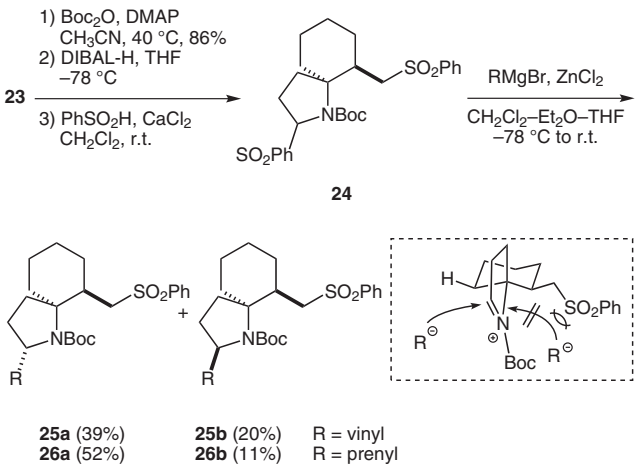
Entry	R	*n*-Bu_3SnH (equiv)	Additive (equiv)	Yield (%)[a]
1	SO_2Ph	0.50	$NaBH_3CN$ (3.0)	51[b]
2	SO_2Ph	2.0	none	60[c] (67[d])
3	CO_2Me	2.0	none	63[e]

[a] Isolated yield.
[b] De-iodinated **13** was isolated in 26% yield.
[c] De-iodinated **13** was isolated in 11% yield.
[d] The reaction was carried out for 6 h in a gram scale.
[e] De-iodinated **19** was isolated in 18% yield.



disfavored TS (W = SO_2Ph) favored TS

Figure 2 Conformational preference



25a (39%) **25b** (20%) R = vinyl
26a (52%) **26b** (11%) R = prenyl

the yields in parenthese are based on a three-step conversion

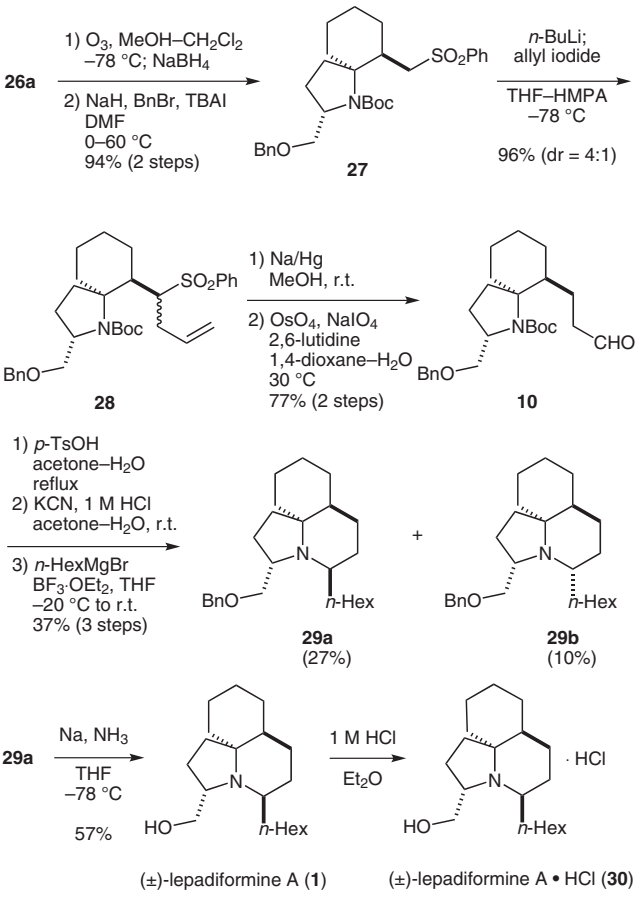
Scheme 5 Stereoselective introduction of the hydroxymethyl group

to determine its relative stereochemistry by X-ray crystallography (Scheme 4).[14] The excellent stereochemical control is explained by taking TS in the 6-*exo* cyclization due to decreased 1,3-diaxial steric repulsion between the vinyl sulfonyl group and benzylic methylene hydrogens (Figure 2).

Having successfully constructed the requisite azaspiro cyclic system, our efforts were then focused on stereoselective introduction of side chains toward (±)-lepadiformine A (Scheme 5). First, lactam **23** was converted into sulfone **24** by Boc protection, partial reduction of imide, and sulfonylation for introduction of the side chain at C-1 position. Unexpectedly, however, it was quite difficult to carry out direct introduction of hydroxymethyl group.[15] Thus, we turned our attention to the construction of the hydroxymethyl group in a stepwise manner.

After survey of various nucleophiles, we found that vinyl Grignard reagents, which are synthetic equivalents of the hydroxymethyl anion, served as appropriate reagents for the additional reaction. Furthermore, the more sterically demanding reagent provided the desired diastereomer in higher selectivity. For instance, while poor facial selectivity was observed with vinyl magnesium bromide giving the diastereomeric mixtures **25a** and **25b** in a ratio of ca. 2:1, a bulky Grignard reagent, such as prenyl Grignard reagent, dramatically improved selectivity up to the ratio of 4.7:1. We anticipated that the stereochemical course of this addition reaction would be governed by the sulfonyl methyl group by blocking the β-face of the acyl iminium ion (Scheme 5).

The prenyl group was converted into a hydroxymethyl group by ozonolysis followed by reductive workup, which was then protected as a benzyl ether (Scheme 6). Elongation of sulfone **27** was executed by allylation at the α-position of sulfone and subsequent reductive removal of sulfone. Then, the terminal olefin was cleaved by Lemieux–Johnson oxidation to provide the known ad-



(±)-lepadiformine A (**1**) (±)-lepadiformine A • HCl (**30**)

Scheme 6 Total synthesis of (±)-lepadiformine A

vanced synthetic intermediate **10**,[16] which was converted into (±)-lepadiformine A (**1**) according to Weinreb's procedure.[5b,d] Finally, treatment of (±)-lepadiformine A (**1**) with 1 M HCl in Et_2O gave the hydrochloride salt **30**, whose physical properties were identical in all aspects to those reported for the natural product.[3]

In conclusion, we have achieved a total synthesis of (±)-lepadiformine A (**1**) featuring a highly diastereoselective radical translocation–cyclization reaction. The cascade radical process enabled us to carry out diastereocontrolled construction of 1-azaspiro[4.5]decane skeleton. Due to the mild and neutral reaction conditions, this strategy is a powerful tool for the synthesis of a variety of azaspirocyclic compounds, which are often involved in bioactive natural products and important medicines.

Acknowledgment

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References and Notes

(1) Current address: Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan.

(2) Current address: Hoshi University, Ebara, Shinagawa-ku, Tokyo 142-8501, Japan.

(3) (a) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691. (b) Sauviat, M.-P.; Vercauteren, J.; Grimaud, N.; Jugé, M.; Nabil, M.; Petit, J.-Y.; Biard, J. F. *J. Nat. Prod.* **2006**, *69*, 558.

(4) Jugé, M.; Grimaud, N.; Biard, J. F.; Sauviat, M.-P.; Nabil, M.; Verbist, J.-F.; Petit, J.-Y. *Toxicon* **2001**, *39*, 1231.

(5) For total syntheses, see: (a) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583. (b) Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett.* **2001**, *3*, 3507. (c) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3511. (d) Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.* **2002**, *67*, 4337. (e) Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3017. (f) Kibayashi, C.; Aoyagi, S.; Abe, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2059. (g) Liu, J.; Hsung, R. P.; Peters, S. D. *Org. Lett.* **2004**, *6*, 3989. (h) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2005**, *127*, 1473. (i) Schär, P.; Renaud, P. *Org. Lett.* **2006**, *8*, 1569. (j) Caldwell, J. J.; Craig, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 2631. (k) Kibayashi, C.; Aoyagi, S.; Abe, H. *J. Synth. Org. Chem. Jpn.* **2007**, *65*, 805. (l) Lygo, B.; Kirton, E. H. M.; Lumley, C. *Org. Biomol. Chem.* **2008**, *6*, 3085. For formal syntheses, see: (m) Lee, M.; Lee, T.; Kim, E.-Y.; Ko, H.; Kim, D.; Kim, S. *Org. Lett.* **2006**, *8*, 745. (n) Mihara, H.; Shibuguchi, T.; Kuramochi, A.; Ohshima, T.; Shibasaki, M. *Heterocycles* **2007**, *72*, 421. (o) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Ohshima, T.; Shibasaki, M. *Chem. Asian J.* **2007**, *2*, 794. For reviews, see: (p) Weinreb, S. M. *Acc. Chem. Res.* **2003**, *36*, 59. (q) Weinreb, S. M. *Chem. Rev.* **2006**, *106*, 2531. (r) Schär, P.; Cren, S.; Renaud, P. *Chimia* **2006**, *60*, 131 . For synthetic studies, see: (s) Pearson, W. H.; Barta, N. S.; Kampf, J. W. *Tetrahedron Lett.* **1997**, *38*, 3369. (t) Pearson, W. H.; Ren, Y. *J. Org. Chem.* **1999**, *64*, 688. For total syntheses of putative lepadiformine, see: (u) Werner, K. M.; de los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 686. (v) Werner, K. M.; de los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 4865. (w) Abe, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2000**, *41*, 1205. (x) Wang, J.; Swidorski, J. J.; Sydorenko, N.; Hsung, R. P.; Coverdale, H. A.; Kuyava, J. M.; Liu, J. *Heterocycles* **2006**, *70*, 423.

(6) (a) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900. (b) For a review on a radical translocation–cyclization reaction, see: Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.* **2001**, *30*, 94.

(7) Takasu, K.; Ohsato, H.; Ihara, M. *Org. Lett.* **2003**, *5*, 3017.

(8) (a) Steffen, S.; Andreas, K. WO 0127122, **2001**. (b) Chloromethylation of *m*-iodoanisole gave some inseparable regioisomers, which were used for the next step without isolation of 2-iodo-4-methoxybenzyl chloride. After benzylation with succinimide, the desired isomer **12** could be separated by recrystallization.

(9) (a) Brown, D. S.; Charreau, P.; Ley, S. V. *Synlett* **1990**, 749. (b) Brown, D. S.; Charreau, P.; Hansson, T.; Ley, S. V. *Tetrahedron* **1991**, *47*, 1311.

(10) Grela, K.; Bieniek, M. *Tetrahedron Lett.* **2001**, *42*, 6425.

(11) (a) *n*-Bu_3SnH (97% purity) was purchased from Aldrich Chemical Company and was used as supplied. AIBN was purchased from Wako Pure Chemical Industries, Ltd. and was used as supplied. Anhydrous benzene was purchased from Kanto Chemical Co., Inc. and was degassed by bubbling with argon gas for 30 min before use.

General Procedure

A three-necked 1000 mL round-bottomed flask fitted with a reflux condenser, an inlet adapter with three-way stopcock, and a septum was charged with starting material **13** (4.8 g, 8.7 mmol). The flask was evacuated and backfilled with argon gas. To the flask was added degassed benzene (300 mL), and the resulting solution was heated at reflux. A benzene solution (20 mL) of AIBN (0.71 g, 4.4 mmol, 0.50 equiv) and *n*-Bu_3SnH (4.7 mL, 17 mmol, 2.0 equiv) was added to the refluxing benzene solution of **13** (0.03 M) over 3 h via a syringe pump, and the reaction mixture was stirred for an additional three hours, after which time TLC (EtOAc) indicated complete consumption of starting material **13**. The solvent was removed under reduced pressure to give a crude material, which was purified by silica gel–KF (10:1) column chromatography[11b] (EtOAc) to afford the desired product **12** (2.5 g, 5.8 mmol, 67%) as a white solid. In the smaller scale reaction, **12** (63.3 mg, 0.152 mmol) was obtained from **13** (139 mg, 0.251 mmol), *n*-Bu_3SnH (135 μL, 0.52 mmol), and AIBN (20.6 mg, 0.126 mmol) in the same way as described in the general procedure; mp 178–179 °C. IR (KBr): 2937, 1682, 1512, 1447, 1408, 1308, 1244, 1148 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85 (dd, 2 H, *J* = 7.5, 1.0 Hz), 7.71–7.65 (m, 1 H), 7.60 (dd, 2 H, *J* = 7.5, 7.5 Hz), 7.17 (d, 2 H, *J* = 8.5 Hz), 6.81 (d, 2 H, *J* = 8.5 Hz), 4.70 (d, 1 H, *J* = 16.0 Hz), 3.80 (s, 3 H), 3.67 (d, 1 H, *J* = 16.0 Hz), 2.88 (dd, 1 H, *J* = 14.0, 1.5 Hz), 2.78 (dd, 1 H, *J* = 14.0, 11.0 Hz), 2.54–2.40 (m, 3 H), 2.32–2.22 (m, 1 H), 1.92–1.83 (m, 1 H), 1.75–1.52 (m, 2 H), 1.61–1.51 (m, 1 H), 1.34–1.18 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.9, 158.6, 139.9, 133.8, 130.6, 129.4, 129.0, 127.8, 113.8, 66.9, 56.4, 55.2, 41.8,

37.8, 37.5, 29.3, 29.1, 25.1, 24.4, 22.9; HRMS (EI$^+$): *m/z* calcd for $C_{24}H_{29}NO_4S$ [M$^+$]: 427.1817; found: 427.1828 (b) Harrowven, D. C.; Guy, I. L. *Chem. Commun.* **2004**, 1968.

(12) A careful inspection of the ^{1}H NMR spectra of the crude material indicated that the trace amount (<5%) of the diastereomer of **12** was observed: however, we could not isolate and identify the diastereomer.

(13) (a) Georg, G. I.; Mashava, P. M.; Akgün, E.; Milstead, M. W. *Tetrahedron Lett.* **1991**, *32*, 3151. (b) Wang, Y.; Babirad, S. A.; Kishi, Y. *J. Org. Chem.* **1992**, *57*, 468.

(14) CCDC 754968 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(15) Bussolo, V. D.; Fiasella, A.; Romano, M. R.; Favero, L.; Pineschi, M.; Crotti, P. *Org. Lett.* **2007**, *9*, 4479.

(16) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217.