JOC Note

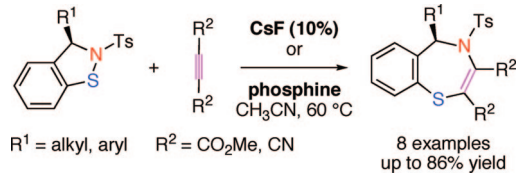
Fluoride Ion and Phosphines as Nucleophilic Catalysts: Synthesis of 1,4-Benzothiazepines from Cyclic Sulfenamides

Cédric Spitz,[†] Jean-François Lohier,[†] Jana Sopkova-de Oliveira Santos,[‡] Vincent Reboul,*[,†] and Patrick Metzner[†]

Laboratoire de Chimie Moléculaire et Thio-organique, ENSICAEN, Université de Caen Basse-Normandie, CNRS; 6, Boulevard du Maréchal Juin, 14050, Caen, France, and Laboratoire de Crystallographie, Centre d'Etudes et de Recherche sur le Médicament de Normandie, Université de Caen Basse-Normandie, 14032 Caen, France

vincent.reboul@ensicaen.fr

Received February 27, 2009

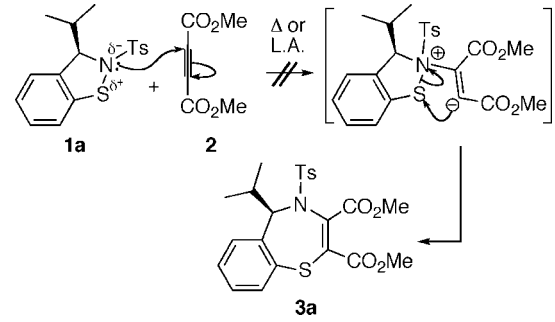


A new methodology, using fluoride ion as a nucleophilic catalyst, was applied for the synthesis of enantiopure 1,4-benzothiazepine from cyclic sulfenamide and electron-deficient acetylene, with high efficiency and atom economy.

Among compounds containing the sulfur−nitrogen bond, sulfenamides are not very popular compared to sulfinamides or sulfonamides. Recently, the chemistry of sulfenamides has received growing attention due to their ease of synthesis[1] and the particular reactivity of this functional group. Indeed, because of the difference in electronegativity, the sulfur atom is considered electrophilic. Moreover, because of the presence of lone electron pairs on both atoms, the nitrogen atom is defined as a "supernucleophile"[2] according to the α-effect.[3]

Consequently, their potential in organic synthesis[4] and their industrial applications have been recognized. For instance, the ability of sulfenamides to form radicals was used to accelerate the vulcanization of rubber. Recently, new reactions involving sulfenamides have emerged: asymmetric sulfenylation[5] of aldehydes and aminosulfenylation[6] of unsaturated aldehydes; oxidation reactions in the presence of NCS;[7] carbonylation[8] or coupling reactions with boronic acids[9] using transition metal. Also of interest is the medicinal applications of sulfenamides: the prodrug omeprazole inhibits the acid-secreting gastric (H^+/K^+)-ATPase involving a sulfenamide as a key intermediate;[10] the water-soluble sulfenamide prodrug carbamazepine;[11] the formation of sulfenamide in enzymes to protect their active site cysteines.[12]

SCHEME 1. Expected Mechanism for the Formation of 3



As part of a program aimed at developing cyclic sulfenamide reactivity,[13] we sought an asymmetric synthesis of 1,4-benzothiazepines,[14] precursor to 1,4-benzothiazepine-1,1-dioxides, which both exhibit a large range of biological activities.[15]

Our initial proposal (Scheme 1) was triggered by the conjugate addition of the nitrogen atom of sulfenamide **1a** to the electron-deficient dimethyl acetylenedicarboxylate **2** (DMAD).

[†] Laboratoire de Chimie Moléculaire et Thio-organique.

[‡] Centre d'Etudes et de Recherche sur le Médicament de Normandie.

(1) (a) Davis, F. A.; Nadir, U. K. *Org. Prep. Proced. Int.* **1979**, *11*, 35. (b) Perrio, S.; Reboul, V.; Metzner, P. In *Science of Synthesis: Compounds with two carbon-heteroatom bonds*; Ramsden, C. A., Ed.; Thieme: Stuttgart, 2007; Vol. 31a, p 1041. (c) Taniguchi, N. *Synlett* **2007**, *12*, 1917.

(2) Welch, W. M. *J. Org. Chem.* **1976**, *41*, 2220.

(3) Buncel, E.; Um, I.-H. *Tetrahedron* **2004**, *60*, 7801.

(4) (a) Heimer, N. E.; Field, L. *J. Org. Chem.* **1970**, *35*, 3012. (b) Davis, F. A. *Int. J. Sulfur Chem.* **1973**, *81*, 71. (c) Craine, L.; Raban, M. *Chem. Rev.* **1989**, *89*, 689.

(5) Sobhani, S.; Fielenbach, D.; Marigo, M.; Wabnitz, T. C.; Joergensen, K. A. *Chem.−Eur. J.* **2005**, *11*, 5689.

(6) Zhao, G.-L.; Rios, R.; Vesely, J.; Ericksson, L.; Córdova, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8468.

(7) Matsuo, J.-i.; Iida, D.; Yamanaka, H.; Mukaiyama, T. *Tetrahedron* **2003**, *59*, 6739.

(8) (a) Kuniyasu, H.; Hiraike, H.; Morita, M.; Tanaka, A.; Sugoh, K.; Kurosawa, H. *J. Org. Chem.* **1999**, *64*, 7305. (b) Knapton, D. J.; Meyer, T. Y. *J. Org. Chem.* **2005**, *70*, 785. (c) Knapton, D. J.; Meyer, T. Y. *Org. Lett.* **2004**, *6*, 687. (d) Rescourio, G.; Alper, H. *J. Org. Chem.* **2008**, *73*, 1612.

(9) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, *4*, 4309.

(10) Shin, J. M.; Cho, Y. M.; Sachs, G. *J. Am. Chem. Soc.* **2004**, *126*, 7800.

(11) Hemenway, J. N.; Nti-Addae, K.; Guarino, V. R.; Stella, V. J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6629.

(12) (a) Sivaramakrishnan, S.; Keerthi, K.; Gates, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 10830. (b) Sarma, B. K.; Mugesh, G. *J. Am. Chem. Soc.* **2007**, *129*, 8872.

(13) Le Fur, N.; Mojovic, L.; Plé, N.; Turck, A.; Reboul, V.; Metzner, P. *J. Org. Chem.* **2006**, *71*, 2609.

(14) Synthesis of 1,4-benzothiazepine core: (a) Fodor, L.; Szabo, J.; Bernath, G.; Parkanyi, L; Sohar, P. *Tetrahedron Lett.* **1981**, *22*, 5077. (b) Kraus, G. A.; Yue, S. *J. Org. Chem.* **1983**, *48*, 2936. (c) Brewer, M. D.; Burgess, M. N.; Dorgan, R. J. J.; Elliott, R. L.; Mamalis, P.; Manger, B. R.; Webster, R. A. B. *J. Med. Chem.* **1989**, *32*, 2058. (d) Nefzi, A.; Ong, N. A.; Giulianotti, M. A.; Ostreh, J. M.; Houghten, R. A. *Tetrahedron Lett.* **1999**, *40*, 4939. (e) Katritzky, A. R.; Xu, Y.-J.; He, H.-Y.; Mehta, S. *J. Org. Chem.* **2001**, *66*, 5590. (f) Neo, A. G.; marcos, C. F.; Marcaccini, S.; Pepino, R. *Tetrahedron Lett.* **2005**, *46*, 7977.

(15) Atherosclerosis: Brieaddy, L. E. WO Patent 016055, 1993. Hyperlipidaemia: (a) Brieaddy, L. E. WO Patent 005188, 1996. (b) Sasahara, T.; Mohri, M. WO Patent 020421, 2004. (c) Starke, I.; Alenfalk, S.; Nordberg, M. P.; Dahlstrom, M. U. J.; Bostrom, S. J. Lemurell, M. A.; Wallberg, A. C. WO Patent 076430, 2004. (d) Sasahara, T.; Mohri, M.; Kasahara, K. I. WO Patent 082874, 2005. (e) Frick, W.; Glombik, H.; Heuer, H.; Schaefer, H.-L.; Theis, S. WO Patent 009655, 2007. Muscle relaxation accelerator: (f) Kaneko, N. WO Patent 105793, 2005. Cell death of cardiac muscles: (g) Kaneko, N.; Oosawa, T.; Sakai, T.; Oota, H. WO Patent 012148, 1992. Diabete: (h) Nagase, T.; Sato, Y.; Eiki, J. WO Patent 053548, 2002. Cardiac hypertrophy: IMarks, A. R.; Lehnart, S. E. WO Patent 021439, 2008. Anti-arrythmic and heart failure: (j) Marks, A. R.; Landry, D. W.; Deng, S.; Cheng, Z. Z. WO Patent 101496, 2006.

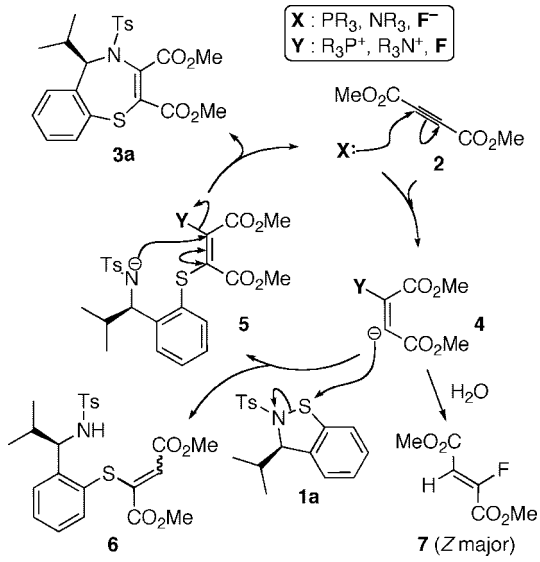
10.1021/jo900449a CCC: $40.75 © 2009 American Chemical Society
Published on Web 04/08/2009

TABLE 1. Optimization of Synthesis of 1,4-Benzothiazepine 3a from 1a

entry	catalyst (mol%)	solvent[a]	Temp (°C)	time (h)	**3a** (% yield)
1	−	CH_3CN	20 to 80	14	0
2	$PdCl_2(PPh_3)_2$ or $RuCl_3 \cdot 3H_2O$ (5)	DMF	40	14	0
3	DPPP (20)	CH_2Cl_2	20	14	12 + **6** (21)
4	DPPP (100)	CH_3CN or toluene	60	14	16 + **6** (21)
5	PMe_3 (100)	CH_2Cl_2	40	14	35
6	PPh_3 (100)	CH_2Cl_2	40	14	70
7	PPh_3 (25)	CH_3CN	60	4	14
8	DABCO (20)	CH_3CN	60	14	21
9	CsF (10)[b]	CH_3CN	20	24	0
10	CsF (200)[b]	CH_3CN	20	4	60
11	CsF (200)[b]	CH_3CN	60	0.5	73
12	CsF (200)	CH_3CN	60	0.5	79
13	CsF (200)	CH_3CN[c]	60	0.5	88
14	CsF (100)	CH_3CN[c]	60	0.5	92
15	CsF (25)	CH_3CN[c]	60	0.5	81
16	CsF (10)[b,d]	CH_3CN[c]	60	2	86

[a] Unless otherwise indicated, all reactions were performed at 0.1 M concentration using 2 equiv of DMAD. [b] 1.1 equiv of DMDA. [c] Concentration = 0.02 M. [d] Slow addition of DMAD over 30 min.

SCHEME 2. Plausible Mechanisms for the Formation of 3a



Subsequent intramolecular 1,3-shift of the sulfur atom would afford the desired seven-membered ring **3a**.[16]

However, no reaction occurred when sulfenamide **1a** was submitted to DMAD in acetonitrile by heating (Table 1, entry 1) or in the presence of Lewis acids (entry 2).

To overcome this problem, we turned to the well-known reactivity of zwitterions **4** generated by nucleophilic addition of phosphine or tertiary amines, as catalyst, to activated unsaturated compounds (Scheme 2; X = PR_3, NR_3; Y = $^+PR_3$, $^+NR_3$).[17] These zwitterions could be able to attack the electrophilic sulfur atom of sulfenamide to lead to intermediate **5**. After an addition/elimination reaction, 1,4-benzothiazepine **3** could be obtained.

Our initial reaction began with diphenylphosphinopropane (DPPP) as catalyst.[18] The expected 1,4-benzothiazepine **3a** was obtained in only 12% yield (Table 1, entry 3) in addition to a 21% of noncyclized product **6** (8/2 *E*/*Z* mixture).[19] A slight improvement was obtained using a stoichiometric amount of DPPP (entry 4). Other phosphines were also tested (entries 5−7). However, only PPh_3 (1 equiv) gave satisfactory 70% yield compared to the dramatically lower yield obtained when using a catalytic amount.[20] An insertion of the phosphine into the S−N bond, affording a pentavalent phosphorus intermediate, could explain these poor results.[21]

The tertiary amine DABCO also initiated the formation of **3a** with a low yield of 21% (entry 8).

Our attention was next turned to the possibility of using fluoride ion as a nucleophilic catalyst (Scheme 2; X = F^-; Y = F). Indeed, CsF is able to react with DMAD **2**, in DMF-water biphasic medium, to afford adduct **7** (*Z* major), after protonation of anion **4** (X = F^-; Y = F).[22] Reaction of **4** with sulfenamide **1a**, followed by an addition−elimination process of intermediate **5** as reported[23] provided 1,4-benzothiazepine **3a** with regeneration of the fluoride anion.

Our first attempt using CsF catalytically (Table 1, entry 9) had disappointing results. The reaction turned black very rapidly indicating polymerization of DMAD. On the other hand, 2 equiv. of CsF furnished **3a** in 60% yield thus validating our concept (entry 10).[24] At 60 °C, the reaction was found to proceed with 73% yield in only 30 min (entry 11). With an increased amount of DMAD (entry 12), a good yield of 79% was obtained. A great improvement was observed when the reaction mixture was diluted (Concentration = 0.02 M) which also allowed us to use a catalytic amount of CsF in the presence of a slight excess of DMAD. After optimization (entries 13−16), **3a** was isolated in an excellent yield of 86% using 10% CsF with slow addition of DMAD (1.1 equiv) by syringe pump.

The reaction was next generalized to sulfenamide **1b** bearing a cyclohexyl substituent (Table 2, entry 1) or an aromatic

(16) Kondo, T.; Baba, A.; Nishi, Y.; Mitsudo, T. *Tetrahedron Lett.* **2004**, *45*, 1469.

(17) For excellent reviews: (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (b) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (c) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, 520. (d) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, 1140.

(18) Sriramurthy, V.; Barcan, G. A.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12928.

(19) The molecular structure of **3a** was confirmed by X-ray crystallographic analysis (see Supporting Information). Interestingly, two conformations were positioned in the unit cell: either the *iso*-propyl group is in a pseudoequatorial or is in a pseudoaxial disposition, as in the molecular structures of sulfenamides **1a** and **1c**.

(20) In CH_2Cl_2 at 40 °C, less than 10% of conversion was observed.

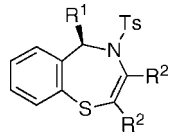
(21) Henke, A.; Srogl, J. *J. Org. Chem.* **2008**, *73*, 7783.

(22) Gorgues, A.; Stéphan, D.; Cousseau, J. *J. Chem. Soc., Chem. Commun.* **1989**, 1493.

(23) Hudlicky, M. *J. Fluorine. Chem.* **1988**, *40*, 99.

(24) **3a** was obtained in 99% ee (Chiral HPLC, Daicel AD).

TABLE 2. Syntheses of 1,4-Benzothiazepines 3, 10 Catalyzed by CsF

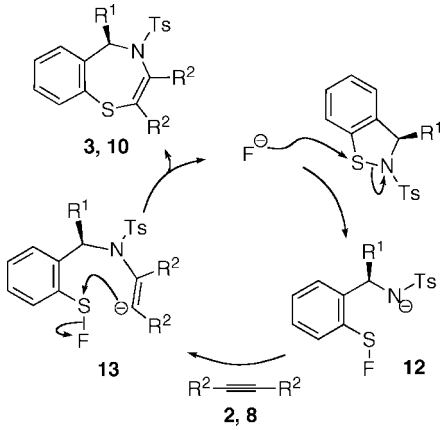


3, 10, 11

entry	R^1	R^2	product	% yield[a]
1	Cy (**1b**)	CO_2Me (**2**)	**3b**	60
2	Ph (**1c**)	CO_2Me (**2**)	**3c**	79
3	3-Br−C_6H_4 (**1d**)	CO_2Me (**2**)	**3d**	65
4	*i*-Pr (**1a**)	CN (**8**)	**10a**	73
5	Cy (**1b**)	CN (**8**)	**10b**	55
6	Ph (**1c**)	CN (**8**)	**10c**	51
7	3-Br−C_6H_4 (**1d**)	CN (**8**)	**10d**	85
8	*i*-Pr (**1a**)	SO_2t-Bu (**9**)	**11a**	0
9	3-Br−C_6H_4 (**1d**)	SO_2t-Bu (**9**)	**11d**	0

[a] All reactions were performed with 10% of CsF in CH_3CN at 60 °C (0.02 M concentration) with slow addition of DMAD over 30 min (1.1 equiv) of acetylene derivative.

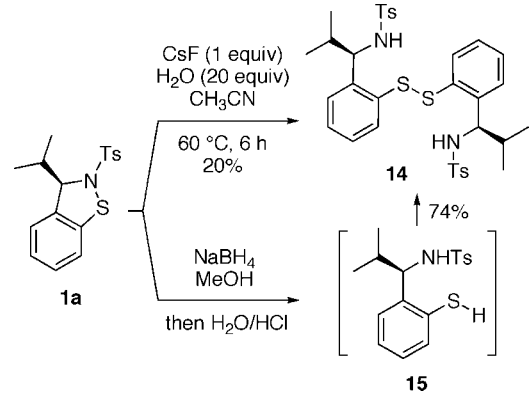
SCHEME 3. Proposed Mechanism for the Formation of 3, 10



substituent (Table 2, entries 2−3).[25] Dicyanoacetylene[26] **8** also were used in this reaction as electron-deficient acetylene and afforded corresponding benzothiazepines **10a-d** (Table 2, entries 4−7) in moderate to good yield. On the other hand, no reaction occurred with di-*t*-butylsulfonylacetylene[27] **9** (Table 2, entries 8−9) and the starting material was recovered.

Although fluoroalkene **7** was always detected in the crude product by ^1H NMR (<5%) when CsF was used as catalyst, we could consider another mechanism, leading to the same compound **3**, also involving the fluoride anion as nucleophilic catalyst (Scheme 3): reaction of fluoride ion with the sulfenamide to generate sulfenyl fluoride **12**; then conjugate addition of amide anion to the electron-deficient acetylene to provide carbanion **13**, which cyclizes into 1,4-benzothiazepine with regeneration of the fluoride anion.

SCHEME 4. Synthesis of Disulfide 14



To investigate the proposed mechanism, the reaction between sulfenamide **1a** and a stoichiometric amount of CsF in acetonitrile was performed.[28] In the presence of water, unstable sulfenyl fluoride **12** should be transformed to corresponding disulfide **14**.[29] Indeed, this compound was isolated in 20% yield (precipitation in the reaction mixture) when a large amount of water was added (Scheme 4).[30] The structure of disulfide **14** was confirmed by reduction of sulfenamide **1a** with $NaBH_4$ into sulfide **15**, followed by aerial oxidation.

To the best of our knowledge, we have demonstrated for the first time the use of fluoride ion as a nucleophilic catalyst.[31] This new methodology was applied for the synthesis of enantiopure 1,4-benzothiazepines with high efficiency and atom economy. Isolation of disulfide provided reasonable evidence for a sulfenyl fluoride as the key intermediate.[32] Further studies with other electrophiles are currently underway.

Experimental Section

Typical Procedure for the Preparation of Benzothiazepines 3, 10 (Table 1, entry 16, 3a as Example). CsF (4.6 mg, 0.03 mmol) was dried under vacuum in a flame-dried round-bottom flask. The sulfenamide **1a** (100 mg, 0.30 mmol) and acetonitrile (12 mL) were added. The resulting suspension was heated at 60 °C and a solution of dimethyl acetylenedicarboxylate **2** (41 μL, 0.33 mmol) in acetonitrile (3 mL) was added over a period of 30 min by syringe pump. The reaction mixture was stirred at 60 °C for 2 h. After filtration of the suspension and evaporation of the solvent, the crude product was purified by column chromatography on silica gel using pentane/Et_2O (8/2) as eluent to yield the corresponding benzothiazepine **3a** (122 mg, 86%) as yellow crystals. R_f: 0.20 (pentane/Et_2O: 8/2); Mp 123−125 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.19 (d, J = 8.4 Hz, 2H, Ar of Ts), 6.98−7.07 (m, 3H, H_6, H_7, H_8), 6.90 (d, J = 8.4 Hz, 2H, Ar of Ts), 6.68 (dd, J = 7.6 Hz, J = 1.5 Hz, 1H, H_9), 4.52 (d, J = 10.8 Hz, 1H, H_5), 3.84 (s, 3H, $MeCO_2$), 3.82 (s, 3H, $MeCO_2$), 2.53−2.58 (m, 1H, CH of *i*-Pr), 2.26 (s, 3H, Me of Ts), 1.34 (d, J = 6.4 Hz, 3H, Me of *i*-Pr), 0.63 (d, J = 6.8 Hz, 3H, Me of *i*-Pr); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 165.8 (C═O), 164.5 (C═O), 143.3 (Ar of Ts), 138.8 (C_{5a}), 135.3 (Ar of Ts), 133.6 (C_2), 132.4 (C_6), 129.2 (C_{9a}), 129.1 (2C, Ar of Ts), 129.0 (C_9), 128.6 (C_3), 127.8 (C_8), 127.6 (2C, Ar of Ts), 126.6 (C_7), 73.7 (C_5), 53.7 ($MeCO_2$), 53.2 ($MeCO_2$), 28.5 (CH of

(25) The ring expansion on the benzylic position was not observed: Voskressensky, L. G.; Akbulatov, S. V.; Borisova, T. N.; Varlamov, A. V. *Tetrahedron* **2006**, *62*, 12392.

(26) This compound was prepared from DMAD in two steps: Hopf, H.; Witulski, B. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Ed.; VCH: Weinheim, 1995; p 60.

(27) This compound was prepared from dichloroacetylene in two steps: (a) Riera, A.; Cabré, F.; Moyano, A.; Pericàs, M. A.; Santamaría, J. *Tetrahedron Lett.* **1990**, *31*, 2169. (b) Riera, A.; Martí, M.; Moyano, A.; Pericàs, M. A.; Santamaría, J. *Tetrahedron Lett.* **1990**, *31*, 2173. Bis(arylsulfonyl)acetylenes were not used due to their instability at room temperature: (c) Pasquato, L.; De Lucchi, O.; Krotz, L. *Tetrahedron Lett.* **1991**, *32*, 2177.

(28) The same reaction in CD_3CN was followed by ^{19}F NMR but, due to problems of solubility, no characteristics signal has been found.

(29) The corresponding thiosulfinate was not observed.

(30) Fifty-five percent of starting material **1a** was recovered.

(31) However, the fluoride ion has been reported as catalyst, in a desilylation-defluorination sequence: Uneyama, K. *J. Fluorine. Chem.* **2007**, *128*, 1087.

(32) It was not possible to trap anion **4** (Y = F) with another electrophile. Indeed, no reaction occurred when DMAD and phenyl-*N*-tosylimine were submittted to CsF in CH_3CN (rt to 80 °C).

i-Pr), 21.6 (Me of Ts), 20.8 (Me of *i*-Pr), 20.6 (Me of *i*-Pr); HRMS (ESI) Calcd for $C_{23}H_{25}NO_6S_2$ (MH^+) *m*/*z* 476.1202, found 476.1216; IR (cm^{-1}): 2950, 1727, 1581, 1435, 1362, 1267, 1164; Anal. Calcd for $C_{23}H_{25}NO_6S_2$: C, 58.09; H, 5.30; N, 2.95; S, 13.48, found C, 58.08; H, 5.39; N, 3.26; S, 13.60. The *ee* was 99% by HPLC (Daicel AD-H column, 1 mL/min, 90/10 *n*-heptane/propan-2-ol, $\lambda = 254$ ηm, $t_R = 23.2$ min, $t_S = 30.4$ min); $[\alpha]^{20}_D = -620$ (c 0.0025, $CHCl_3$).

Acknowledgment. We thank the "Région Basse-Normandie", the "Ministère de la Recherche", CNRS (Centre National de la Recherche Scientifique), the European Union (FEDER funding) for financial support.

Supporting Information Available: Experimental procedures and characterization for all new compounds described in this work, crystallographic data for the reported structures (CIF format). This material is available free of charge via the Internet at http://pubs.acs.org.

JO900449A