Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 835–839
Tetrahedron Letters

Microwave assisted ring-opening of epoxides with *N*-biaryl sulfonamides in the synthesis of matrix metalloproteinase-9 inhibitors

Shyh-Ming Yang *, William V. Murray

Johnson & Johnson Pharmaceutical Research and Development, L.L.C., 8 Clarke Drive, Cranbury, NJ 08512, USA

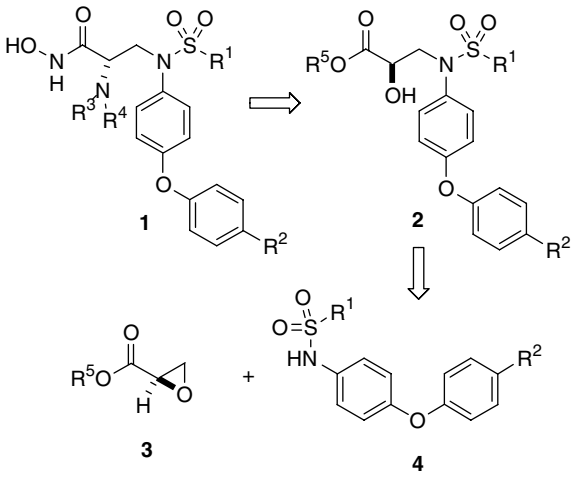
Received 20 July 2007; revised 27 November 2007; accepted 29 November 2007
Available online 4 December 2007

Abstract

A microwave accelerated epoxide ring-opening process with *N*-biaryl sulfonamides is described. Under this mild, highly efficient condition, an α-hydroxy-β-*N*-biaryl sulfonamide skeleton is rapidly assembled leading ultimately to a novel series of matrix metalloproteinase-9 inhibitors with single digit nanomolar activities.
© 2007 Elsevier Ltd. All rights reserved.

Keywords: Microwave; Ring-opening; Epoxide; Sulfonamide; Matrix metalloproteinase; MMP

Ring opening of epoxides with diverse nucleophiles is an important transformation in organic synthesis that generates a variety of useful building blocks with hydroxyl functionalities.[1] In our small molecule drug design program, we were particularly interested in synthesizing a novel skeleton, **1** to serve as matrix metalloproteinase-9 (MMP-9) inhibitors (Scheme 1).[2] We envisioned how this skeleton could be derived easily from **2** by a S_N2 replacement of its activated α-hydroxyl group. More importantly, this skeleton with diverse substitutions on the sulfonamide and/or biaryl ether portion could be rapidly assembled by an epoxide ring-opening reaction from common epoxides **3** and simple sulfonamides **4**. A few reports on ring opening of epoxides with *N*-aryl toluenesulfonamides employing thermal condition in the presence of a phase transfer reagent have been previously documented.[3] These conditions were suitable for the synthesis of benzo-fused heterocycles.[3,4] To diversify structure rapidly for structure–activity relationship (SAR) studies, we herein report a microwave accelerated ring opening of epoxides with *N*-biaryl sulfonamides, particularly the alkanesulfonamides, for the synthesis of an α-hydroxy-β-*N*-biaryl sulfonamide skeleton.[5] Elaboration of these intermediates ultimately led to a novel series of MMP-9 inhibitors.



Scheme 1.

Epoxide **5a** together with sulfonamide **6a** were initially selected to evaluate the effectiveness of this process.

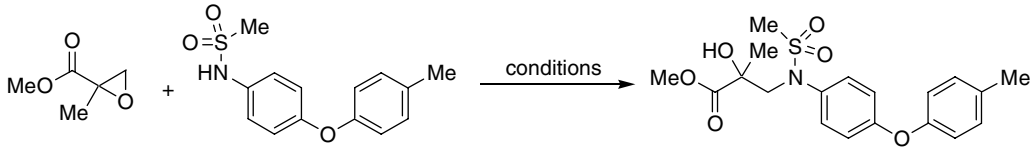
* Corresponding author. Tel.: +1 609 409 3491; fax: +1 609 655 6930.
E-mail address: syang9@prdus.jnj.com (S.-M. Yang).

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.11.184

Conditions including bases, solvents, concentrations, and reaction temperatures were screened under microwave irradiation and/or thermal condition (Table 1). The conversion of **6a** was determined by HPLC analysis using 4-bromobiphenyl as the internal standard. By using K_2CO_3 as the base and DMF as the solvent, ring opening proceeded rapidly with high conversion (84%) in 20 min at 120 °C under microwave irradiation (entry 1). Under these reaction conditions, the use of Cs_2CO_3 as the base or DMSO as the solvent, proved to be slightly less effective (68–72% conversion, entries 2 and 3). Elevated reaction temperatures at 140–160 °C did increase the conversion to 95% in 10–20 min (entries 4 and 5). However, some undesired products were observed based on the HPLC analysis. It was also found that higher concentrations provided excellent conversion (95%) (entry 6 vs entry 1). Under this concentration (0.5 M), 84% conversion could be obtained at a lower temperature (90 °C) with a 40 min irradiation (entry 7). A reaction utilizing a catalytic amount of base (K_2CO_3, 0.2 equiv) and a phase transfer reagent ($BnEt_3N^+Cl^-$, 0.1 equiv) in 1,4-dioxane was also investigated under microwave condition. However, only 46% conversion was obtained after 30 min irradiation (entry 8). Under a similar irradiation, the conversion increased significantly to 85% within 20 min by using stoichiometric amount of K_2CO_3 (entry 9). In contrast, thermal conditions with a catalytic amount of K_2CO_3 in dioxane, only gave 30% conversion after 1 h of heating (entry 10).[3] Indeed, high conversion could be achieved by using 1.0 equiv of base with a longer reaction time (6 h, entry 11). Although the higher reaction temperature (120 °C) also accelerated the reaction rate, several undesired products were observed based on the HPLC results (entry 12).

With the optimized condition in hand, our attention was next focused on exploring the scope and limitation of this process. Diverse epoxides **5** and *N*-biaryl sulfonamides **6** with various R^1 and R^2 substituents were evaluated using the conditions established above, namely K_2CO_3 (1.0–2.0 equiv) as the base in DMF (0.25–0.5 M) under microwave irradiation (Table 2).[6] Under this condition, the ring opening of **5a** with **6a** gave **7** in 88% isolated yield after 20 min irradiation at 120 °C (entry 1). This result was consistent with that observed during the optimization procedure described above. By applying the thermal conditions for 12 h, a comparable yield of **7** (76%) was obtained (entry 2). It is worth to note that a lower temperature with prolonged irradiation is particularly suitable for volatile epoxides such as methyl glycidate **5b**. For instance, treatment of **6a** with (*R*)-**5b** and (*S*)-**5b** at 80 °C for 40 min afforded (*R*)-**9a** and (*S*)-**9a** (85% and 82%, respectively, entries 3 and 4). The reaction of TBS-protected glycidol **5c** with **6c** provided diol **10** in 78% yield after deprotection using tetrabutyl-

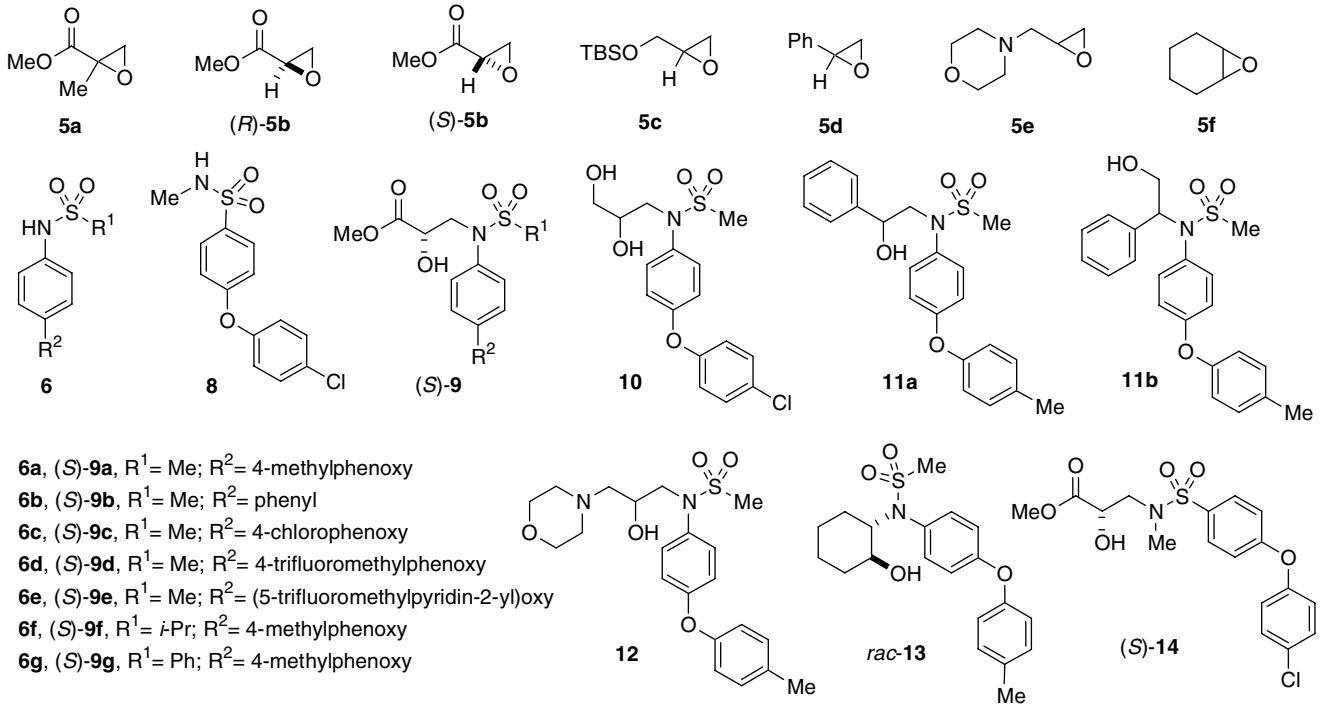
Table 1
Ring opening of epoxide **5a** with sulfonamide **6a**[a]



Entry	Base	Solvent	Concd of **6a** (M)	Condition	Temperature (°C)	Conv. of **6a**[b] (10 min)	Conv. of **6a**[b] (20 min)	Conv. of **6a** (time)
1	K_2CO_3	DMF	0.1	Microwave	120	65	84	—
2	Cs_2CO_3	DMF	0.1	Microwave	120	68	68	—
3	K_2CO_3	DMSO	0.1	Microwave	120	62	72	—
4	K_2CO_3	DMF	0.1	Microwave	140	79	95[c]	—
5	K_2CO_3	DMF	0.1	Microwave	160	95[c]	—	—
6	K_2CO_3	DMF	0.5	Microwave	120	—	>95	—
7	K_2CO_3	DMF	0.5	Microwave	90	—	65	84 (40 min)
8[d]	K_2CO_3 (0.2 equiv)	1,4-Dioxane	0.5	Microwave	120	—	—	46 (30 min)
9[d]	K_2CO_3 (1.0 equiv)	1,4-Dioxane	0.5	Microwave	120	—	85	—
10[d]	K_2CO_3 (0.2 equiv)	1,4-Dioxane	0.5	Thermal	90	—	30 (1 h)	—
11[d]	K_2CO_3 (1.0 equiv)	1,4-Dioxane	0.5	Thermal	90	—	68 (2 h)	>90 (6 h)
12[d,e]	K_2CO_3 (1.0 equiv)	1,4-Dioxane	0.5	Thermal	120	—	60 (1 h)[c]	86 (3 h)[c]

[a] All reactions employed **5a** (2.0 equiv), **6a** (1.0 equiv), and base (2.0 equiv) unless otherwise specified.
[b] Conversions of **6a** were determined by HPLC analysis at 10 and/or 20 min using 4-bromobiphenyl as the internal standard unless otherwise specified.
[c] Side products formed by HPLC.
[d] Additive, $BnEt_3N^+Cl^-$ (0.1 equiv), was employed.
[e] The reaction was performed in a sealed tube.

Table 2
Synthesis of **7**, **9**–**14** via ring opening of epoxides **5** with biaryl sulfonamides **6** and **8**[a]



Entry	Epoxide	Sulfonamide	Temperature (°C)	Time (min)	Product (yield, %)
1	**5a**	**6a**	120	20	**7** (88)
2[b]	**5a**	**6a**	90	12 h	**7** (76)
3	(*R*)-**5b**	**6a**	80	40	(*R*)-**9a** (85)
4	(*S*)-**5b**	**6a**	80	40	(*S*)-**9a** (82)
5	**5c**	**6c**	100	30	**10** (78)[c]
6	**5d**	**6a**	120	30	**11a** (68) + **11b** (4)
7	**5e**	**6a**	140	30	**12** (88)
8[d]	**5f**	**6a**	180	90	*rac*-**13** (67)
9	(*S*)-**5b**	**6b**	80	40	(*S*)-**9b** (86)
10	(*S*)-**5b**	**6c**	80	40	(*S*)-**9c** (78)
11	(*S*)-**5b**	**6d**	80	40	(*S*)-**9d** (75)
12	(*S*)-**5b**	**6e**	80	40	(*S*)-**9e** (72)
13	(*S*)-**5b**	**6f**	80	40	(*S*)-**9f** (75)
14	(*S*)-**5b**	**6g**	80	40	(*S*)-**9g** (71)
15	(*S*)-**5b**	**8**	80	60	(*S*)-**14** (38)
16[b]	(*S*)-**5b**	**8**	90	24 h	(*S*)-**14** (47)

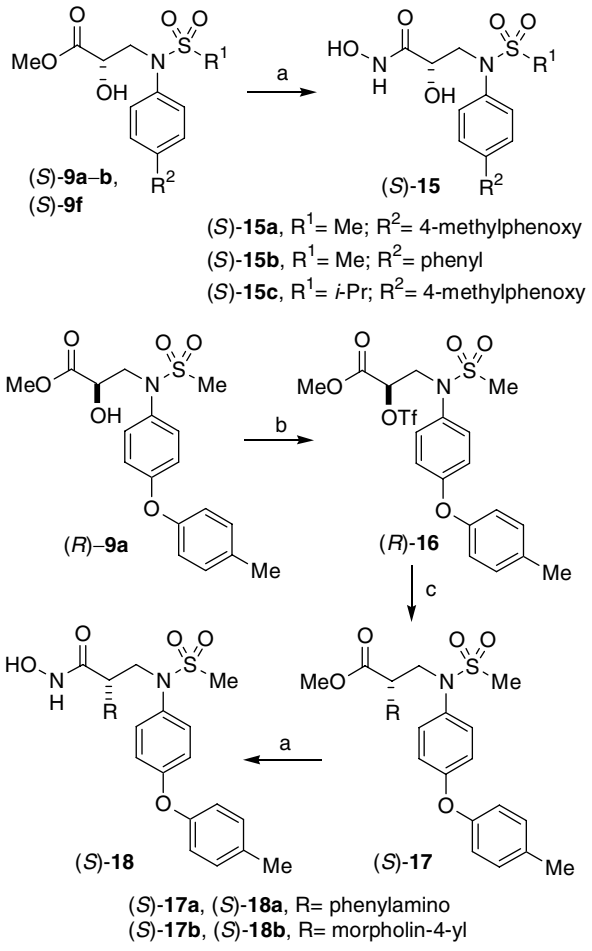
[a] Epoxide (2.0–3.0 equiv), sulfonamide (1.0 equiv), and K_2CO_3 (1.0–2.0 equiv) in DMF (0.5–0.25 M) were employed under microwave irradiation with indicated temperature and reaction time unless otherwise specified.
[b] Epoxide (2.0–3.0 equiv), sulfonamide (1.0 equiv), K_2CO_3 (1.0–2.0 equiv), and $BnEt_3N^+Cl^-$ (0.1 equiv) in 1,4-dioxane (0.5–0.25 M) were employed under thermal heating condition.
[c] Yield after deprotection using TBAF in THF.
[d] Microwave condition with DMSO as the solvent was employed.

ammonium fluoride (TBAF) in THF (entry 5). Moreover, ring opening of epoxides **5d**,**e** with **6a** gave structurally diversified hydroxyl compounds **11a** and **12** (70–88%, entries 6 and 7). With the epoxides examined, the ring opening typically occurred at the sterically less hindered carbon with an exception of the styrene oxide **5d**. A small amount of regio-isomer **11b** (4%) was also isolated (Table 2, entry 6).[7] Initial attempts to open sterically hindered epoxides, such as **5f**, by a similar microwave irradiation or under thermal heating conditions were fruitless. In fact, harsher conditions, that is, using DMSO as the solvent at 180 °C for 1.5 h irradiation, were required to promote this reaction successfully with 67% of **13** isolated (entry 8).[8]

The effect of substituents on both sulfonamide (R^1) and on the *N*-phenyl ring (R^2) was next examined. The ring-opening of (*S*)-**5b** with **6b**–**e**, which contained an aryl or aryl ether at 4-position, afforded (*S*)-**9b**–**e** in 72–86% (entries 9–12). These results suggested only a marginal influence by the R^2 substituent. Indeed, a minor influence of steric and/or electronic effect on sulfonamide (R^1) was

also observed. For example, when isopropanesulfonamide **6f** and benzenesulfonamide **6g** were employed, comparable yields of products (*S*)-**9f** and (*S*)-**9g** were obtained (71–75%, entries 13 and 14). Notably, by switching the *N*-biaryl mathanesulfonamide (e.g., **6c**) to a *N*-methyl biaryl sulfonamide (e.g., **8**), a relatively low yield of (*S*)-**14** was obtained under either microwave or thermal conditions presumably due to the significantly reduced NH acidity (entries 15 and 16 vs entry 10).

After complete examination of this process, the products (*S*)-**9a**,**b** and (*S*)-**9f** derived from the ring-opening reaction were converted to the corresponding hydroxamic acids (*S*)-**15a**–**c** in 73–95% yield upon treatment with hydroxylamine hydrochloride salt and sodium methoxide (Scheme 2).[9] As previously addressed, the α-hydroxyl group is perfectly situated for installation of diverse amino groups by a S_N2 displacement. Activation of the hydroxyl group of (*R*)-**9a** with triflic anhydride using 2,6-lutidine as the base provided intermediate (*R*)-**16**, which could undergo facile displacement with various amines.[10] For instance, treatment of (*R*)-**16** with aniline or morpholine gave (*S*)-**17a**,**b** in excellent yields (84–89%). Finally, the hydroxamic acids (*S*)-**18a**,**b** were obtained by a similar transformation as mentioned above for (*S*)-**15**, though only a moderated yield of (*S*)-**18b** (38%) was obtained.



Scheme 2. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$ (2.0 equiv), NaOMe (6.0 equiv), MeOH, rt, 1 h, **15a** (1 h, 84%), **15b** (1 h, 73%), **15c** (1 h, 95%), **18a** (3 h, 86%), **18b** (24 h, 38%); (b) Tf_2O (1.2 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2, −20 to 0 °C, 1 h, 91%; (c) $PhNH_2$ or morpholine (4.0 equiv), CH_2Cl_2, 0 °C to rt, **17a** (24 h, 84%), **17b** (1 h, 89%).

The inhibitory activities of hydroxamates (*S*)-**15a**–**c** and (*S*)-**18a**,**b** were assayed against the MMP-9 enzyme. Preliminary SAR results showed that the biphenyl ether ((*S*)-**15a**) was a suitable substituent on the nitrogen atom, giving an IC_{50} of 7.8 nM, whereas the biphenyl substituent ((*S*)-**15b**) only provided 79% inhibition at 10 μM. Increased steric influence on R^1, such as isopropyl ((*S*)-**15c**), resulted ca. 35-fold loss of activity (286 nM). Instead of an α-hydroxyl group, the α-amino substituents, including phenylamino and morpholin-4-yl ((*S*)-**18a**,**b**), both gave increased potency at low single digit nanomolar range (0.6 nM and 1.9 nM for (*S*)-**18a** and (*S*)-**18b**, respectively).

In conclusion, a facile microwave assisted epoxide ring-opening reaction with *N*-biaryl sulfonamides has been described. As illustrated by all examples examined, this reaction is extremely efficient with good isolated yields and general for both reaction partners. The skeleton assembled by this ring-opening process could be elaborated to its hydroxamic acid that exhibited significant binding affinity toward MMP-9 enzyme. The optimization and detailed SAR studies of this series as novel MMP-9 inhibitors will be disclosed in due course.

Acknowledgments

S.-M.Y. thanks Dr. Maud Urbanski for helpful discussion upon preparing this manuscript and Ms. Bingbing Wang for preparation of compound (*S*)-**15c**. The authors also thank Dr. Robert Scannevin for the potency determination of selected compounds.

Supplementary data

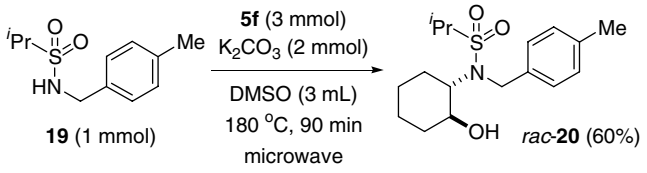
The microwave parameters, representative procedures, detailed reaction conditions of epoxide ring-opening reactions, and ^1H NMR spectra of selected compounds are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.184.

References and notes

1. For representative examples, see: (a) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis I–III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999; Vol. 3, pp 1306–1326; (b) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421–431.
2. In the design of sulfonamide-based MMP inhibitors, typically, the biaryl ether potion was attached to the sulfonyl group instead of on the nitrogen atom. Few exceptions, see: (a) Cherney, R. J.; Mo, R.; Meyer, D. T.; Hardman, K. D.; Liu, R.-Q.; Covington, M. B.; Qian, M.; Wasserman, Z. R.; Christ, D. D.; Trzaskos, J. M.; Newton, R. C.; Decicco, C. P. *J. Med. Chem.* **2004**, *47*, 2981–2983; (b) Kim, S.-H.; Pudzianowski, A. T.; Leavitt, K. J.; Barbosa, J.; McDonnell, P. A.;

Metzler, W. J.; Rankin, B. M.; Liu, R.; Vaccaro, W.; Pitts, W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1101–1106.

3. (a) Albanese, D.; Landini, D.; Lupi, V.; Penso, M. *Ind. Eng. Chem. Res.* **2003**, *42*, 680–686; and references cited therein; (b) Cleator, E.; Sheen, F. J.; Bio, M. M.; Brands, K. M. J.; Davies, A. J.; Dolling, U. H. *Tetrahedron Lett.* **2006**, *47*, 4245–4248.
4. An example on intramolecular cyclization using trifluoroacetic acid, see: Goujon, J.-Y.; Zammattio, F.; Chrětien, J. M.; Beaudet, I. *Tetrahedron* **2004**, *60*, 4037–4049.
5. Representative examples on microwave assisted epoxide opening with other nucleophiles, see: (a) Kureshy, R. I.; Singh, S.; Khan, N. H.; Abdi, S. R.; Agrawal, S.; Mayani, V. J.; Jasra, R. V. *Tetrahedron Lett.* **2006**, *47*, 5277–5279; (b) Glas, H.; Thiel, W. R. *Tetrahedron Lett.* **1998**, *39*, 5509–5510; (c) Khalafi-Nezhad, A.; Soltani Rad, M. N.; Khoshnood, A. *Synthesis* **2004**, 583–589; (d) Desai, H.; D'Souza, B. R.; Foether, D.; Johnson, B. F.; Lindsay, H. A. *Synthesis* **2007**, 902–910.
6. *Representative procedure*: In a microwaveable tube were placed **6a** (277 mg, 1.0 mmol) and K_2CO_3 (276 mg, 2.0 mmol). Then, DMF (2 mL) and (*S*)-**5b** (306 mg, 3.0 mmol) were added sequentially. The tube was sealed and was heated at 80 °C for 40 min under microwave irradiation. The mixture was then poured into Et_2O/H_2O (30 mL/30 mL). The organic layer was washed with saturated $NH_4Cl_{(aq)}$ (30 mL), brine (30 mL), dried (Na_2SO_4), and then filtered. After removal of solvent, the crude product was purified by silica gel chromatography using EtOAc/hexane (1/4–3/7) as the eluent to give 310 mg of (*S*)-**9a** (82%) as a pale brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, $J = 8.0$ Hz, 2H), 7.17 (d, $J = 8.0$ Hz, 2H), 6.97 (d, $J = 8.0$ Hz, 2H), 6.94 (d, $J = 9.0$ Hz, 2H), 4.30–4.26 (m, 1H), 4.06–3.94 (m, 2H), 3.69 (s, 3H), 3.00 (s, 3H), 2.99 (s, 1H, OH), 2.35 (s, 3H); MS (EI) 402 (M^++Na, 100), 380 (M^++1, 60). Anal. Calcd for $C_{18}H_{21}NO_6S$: C, 56.98; H, 5.58; N, 3.69. Found: C, 56.88; H, 5.54; N, 3.61.
7. The ratio of **11a/11b** was ca. 16/1 based on the ^{1}H NMR analysis of the crude mixture. The ring opening of styrene oxide usually associates with the regioselectivity issue. Some examples see: Placzek, A. T.; Donelson, J. L.; Trivedi, R.; Gibbs, R. A.; De, S. K. *Tetrahedron Lett.* **2005**, *46*, 9029–9034; and Refs. 3a and 5d.
8. Under the same irradiation using DMF as the solvent, 55% isolated yield of **13** was obtained. Under a thermal condition (90 °C, 24 h) or a microwave condition (DMF, 120 °C, 40 min), low conversion (<15%) was observed. In addition, the microwave condition (DMSO, 180 °C, 90 min) was also able to promote the ring opening of **5f** with *N*-(4-methylphenyl)methyl 2-propanesulfonamide **19** to afford *rac*-**20** (60%).



9. The condition was adopted from MacPherson, L. J.; Bayburt, E. K.; Capparelli, M. P.; Carroll, B. J.; Goldstein, R.; Justice, M. R.; Zhu, L.; Hu, S.; Melton, R. A.; Fryer, L.; Goldberg, R. L.; Doughty, J. R.; Spirito, S.; Blancuzzi, V.; Wilson, D.; O'Byrne, E. M.; Ganu, V.; Parker, D. T. *J. Med. Chem.* **1997**, *40*, 2525–2532.
10. (a) Kogan, T. P.; Somers, T. C.; Venuti, M. C. *Tetrahedron* **1990**, *46*, 6623–6632; (b) Uenishi, J.; Hamada, M.; Aburatani, S.; Matsui, K.; Yonemitsu, O.; Tsukube, H. *J. Org. Chem.* **2004**, *69*, 6781–6789.