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A New Strategy for the Synthesis of 1,4-Benzodiazepine Derivatives Based on the Tandem *N*-Alkylation−Ring Opening−Cyclization Reactions of Methyl 1-Arylaziridine-2-carboxylates with *N*-[2-Bromomethyl(phenyl)]trifluoroacetamides

Jin-Yuan Wang, Xue-Fei Guo, De-Xiang Wang, Zhi-Tang Huang, and Mei-Xiang Wang*

Beijing National Laboratory for Molecular Sciences, Laboratory of Chemical Biology, Institute of Chemistry, Chinese Academy of Sciences, Beijing, 100080, China

mxwang@iccas.ac.cn

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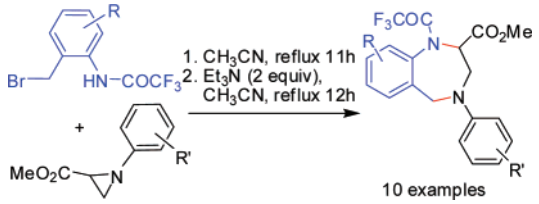

A new method for the synthesis of novel 1,4-benzodiazepine derivatives has been established from a one-pot reaction of methyl 1-arylaziridine-2-carboxylates with *N*-[2-bromomethyl(aryl)]trifluoroacetamides. The reaction proceeds through the *N*-benzylation and highly regioselective ring-opening reaction of aziridine by bromide anion followed by Et_3N-mediated intramolecular nucleophilic displacement of the bromide by the amide nitrogen. The easy availability of starting materials, simple and convenient synthetic procedure, and formation of functionalized 1,4-benzodiazepine scaffold ready for further chemical manipulations render this strategy useful in synthetic and medicinal chemistry.

1,4-Benzodiazepines are one of the most important and widely used scaffolds in medicinal chemistry.[1] A large number of 1,4-benzodiazepine derivatives, for example, have been found to act as anxiolytic, anticonvulsant, and antihypnotic agents,[2] selective cholecystokinin (CCK) receptor subtype A or B antagonists,[3] platelet-activating factor antagonists,[4] human immunodeficiency virus (HIV) transactivator Tat antagonists,[5] and reverse transcriptase inhibitors.[6] To further discover molecules with potent and selective biological activity, it is of importance to explore new methodology for the synthesis of novel 1,4-benzodiazepine entities. A few synthetic approaches to 1,4-benzodiazepine skeletons have been reported in literature, and the most frequently employed methods include (A) the reaction of 2-aminobenzoic acids and their derivatives or 2-aminobenzophone derivatives **1** with α-amino acid derivatives,[7] (B) the cyclocondensation of 2-halobenzoic acids and their derivatives or 2-halobenzophone derivatives **2** with diamine derivatives,[8] and (C) the reaction of diamines **3** with bis-electrophiles[9] (Scheme 1). The Pictet−Spengler reaction of **4** with aldehydes was also used to yield 1,4-benzodiazepine structure[10] (D, Scheme 1). On the basis of oxidative formation of electrophilic *N*-acylnitrenium from amide **5**, Tellitu, Dominguez, and their co-workers[11] recently introduced an aromatic amidation route to 1,4-benzodiazepine derivatives (E, Scheme 1).

As a three-membered-ring heterocycle, aziridine compounds show interesting and diverse reactivity, and they have become useful synthons in organic synthesis.[12] The *C*-activated aziridine compounds such as aziridine-2-carboxylic acid derivatives and aziridine-2-phosphonates, for example, have been reported to undergo various ring-opening reactions and reactions on both nitrogen and carbon atoms of the ring, producing a large number of functionalized organic molecules that are not easily accessible

(1) (a) Neamati, N.; Turpin, J. A.; Winslow, H. E.; Chrisensen, J. L.; Williamson, K.; Orr, A.; Rice, W. G.; Pommier, Y.; Garofalo, A.; Brizzi, A.; Campiani, G.; Fiorini, I.; Nacci, V. J. *J. Med. Chem.* **1999**, *42*, 3334. (b) Garofalo, A.; Balconi, G.; Botta, M.; Corelli, F.; DIncalci, M.; Fabrizi, G.; Fiorini, I.; Lamba, D.; Nacci, V. *Eur. J. Med. Chem.* **1993**, *28*, 213. (c) Grunewald, G. L.; Dahanukar, V. H.; Ching, P.; Criscione, K. R. *J. Med. Chem.* **1996**, *39*, 3539. (d) Hoffmann-La Roche, A. C. F. & Co., Netherlands Patent 6 500 817, 1964. (e) Toshiyuki, H.; Takuhiro, I.; Hisao, Y. Japanese Patent 7 272 107, 1972.

(2) Sternbach, L. H. *J. Med. Chem.*, **1979**, *22*, 1.

(3) Bock, M. G.; DiPardo, R. M.; Evans, B. E.; Rittle, K. E.; Whitter, W. L.; Veber, D. E.; Anderson, P. S.; Freidinger, R. M. *J. Med. Chem.*, **1989**, *32*, 13.

(4) Kornecki, E.; Ehrlich, Y. H.; Lenox, R. H. *Science*, **1984**, *226*, 1454.

(5) Hsu, M.-C.; Schutt, A. D.; Hooly, M.; Slice, L. W.; Sherman, M. I.; Richman, D. D.; Potash, M. J.; Volsky, D. J. *Science*, **1991**, *254*, 1799.

(6) Pauwels, R.; Andries, K.; Desmyter, J.; Schols, D.; Kukla, M. J.; Breslin, H. J.; Raeymaeckers, A.; van Gelder, J.; Woestenborghs, R.; Heykants, J.; Schellekens, K.; Jannsen, M. A.; Clerq, E. D.; Janssen, P. A. *J. Nature* (*London*) **1990**, *343*, 470.

(7) (a) Blazevic, N.; Kajfez, F. *J. Heterocycl. Chem.* **1971**, *8*, 845. (b) Sugasawa, T.; Adachi, M.; Toyoda, T.; Sasakura, K. *J. Heterocycl. Chem.* **1979**, *16*, 445. (c) Castro, J. L.; Broughton, H. B.; Russell, M. G. N.; Rathbone, D.; Watt, A. P.; Ball, R. G.; Chapman, K. L.; Patel, S.; Smith, A. J.; Marshall, G. R.; Matassa, V. G. *J. Med. Chem.* **1997**, *40*, 2491. (d) Anzini, M.; Canullo, L.; Braile, C.; Cappelli, A.; Callelli, A.; Vomero, S.; Menziani, M. C.; De Benedetti, P. G.; Rizzo, M.; Collina, S.; Azzolina, O.; Sbacchi, M.; Chelardini, C.; Galeotti, N. *J. Med. Chem.* **2003**, *46*, 3853. (e) Nadin, A.; Sanchez Lopez, J. M.; Owens, A. P.; Howells, D. M.; Talbot, A. C.; Harrison, T. *J. Org. Chem.* **2003**, *68*, 2844. (f) Herrero, S.; Garcia-Lopez, M. T.; Herranz, R. *J. Chem. Org.* **2003**, *68*, 4582. (g) Herrero, S.; Garcia-Lopez, M. T.; Cenarruzabeitia, E.; Del Rio, J.; Herranz, R. *Tetrahedron* **2003**, *59*, 4491. (h) Kamal, A.; Ramana, A. V.; Reddy, K. S.; Remana, K. V.; Babu, A. H.; Prasad, B. R. *Tetrahedron Lett.* **2004**, *45*, 8187. (i) Marcaccini, S.; Miliciani, M.; Pepino, R. *Tetrahedron Lett.* **2005**, *46*, 711. (j) Kraus, G. A.; Maeda, H. *Tetrahedron Lett.* **1994**, *35*, 9189. (k) Griesbeck, A. G.; Kramer, W.; Lex, J. *Synthesis* **2001**, 1159.

(8) Breslin, H. J.; Kukla, M. J.; Ludovici, D. W.; Mohrbacher, R.; Ho, W.; Miranda, M.; Rodgers, T. K.; Leo, G.; Gauthier, D. A.; Ho, C. Y.; Scott, M. K.; De Clercq, E.; Pauwels, R.; Andries, K.; Janssen, M. A. C.; Janssen, P. A. *J. Med. Chem.* **1995**, *38*, 771.

(9) (a) Boyer, S. K.; Fitchett, G.; Wasley, J. W. F.; Zaunius, G. *J. Heterocycl. Chem.* **1984**, *21*, 833. (b) Massa, S.; Mai, A.; Artico, M. *Tetrahedron* **1989**, *45*, 2763. (c) Hone, N. D.; Wilson, W.; Reader, J. C. *Tetrahedron Lett.* **2003**, *44*, 8493. (d) Hamann, L. G.; Ding, C. Z.; Miller, A. V.; Madsen, C. S.; Wang, P.; Stein, P. D.; Pudzianowski, A. T.; Green, D. W.; Monshizadegan, H.; Atwal, K. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1031. (e) Al-Awar, R. S.; Ray, J. E.; Hecker, K. A.; Joseph, S.; Huang, J.; Shih, C.; Brooks, H. B.; Spencer, C. D.; Watkins, S. A.; Schultz, R. M.; Considine, E. L.; Faul, M. M.; Sullivan, K. A.; Kolis, S. P.; Carr, M. A.; Zhang, F. *Bioorg. Med. Chem. Lett.* **2004**, *24*, 3925.

(10) (a) Katrizky, A. R.; Xu, Y.-J.; He, H.-Y. *J. Chem. Soc., Perkin Trans. 1* **2002**, 592. (b) Welmaker, G. S.; Sabalski, J. E. *Tetrahedron Lett.* **2004**, *45*, 4581.

(11) Herrero, M. T.; Tellitu, I.; Dominguez, E.; Moreno, I.; SanMartin, R. *Tetrahedron Let.* **2002**, *43*, 8273.

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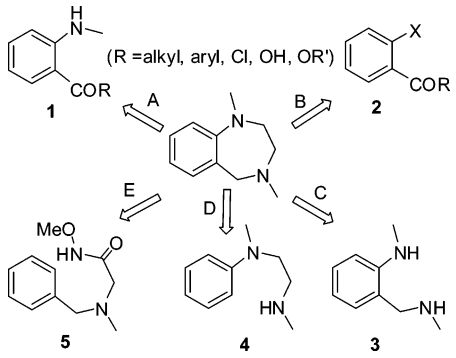
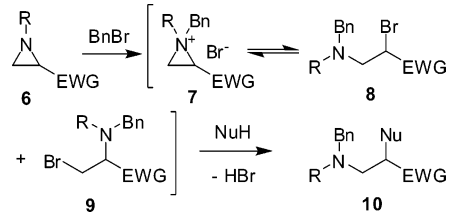
SCHEME 1. Reported Synthetic Approaches to 1,4-Benzodiazepine Derivatives



SCHEME 2. Highly Regioselective Ring Opening Reaction of *C*-Activated Aziridines with Benzyl Bromide and a Nucleophile



by other means. Very recently, we[13] and other research groups[14] have revealed that aziridine-2-carboxylic acid derivatives **6** are able to react with benzyl bromide to give a mixture of ring-opening products **8** and **9**. Treatment of the mixture with nucleophilic agents such as an amine led to the formation of vicinal diamine products **10**. The exclusive formation of **10** indicated an equilibrium of **8** and **9** with aziridinium species **7** (Scheme 2).

We envisioned that, instead of using consecutively benzyl bromide and amine, the employment of a bifunctional reactant containing both electrophilic and nucleophilic sites in such a reaction as depicted in Scheme 2 would result in the formation of *N*-heterocyclic products. Herein we report a novel and very convenient synthesis of new 1,4-benzodiazepine derivatives from the reaction of 1-arylaziridine-2-carboxylates with *N*-[2-bromomethyl(aryl)]trifluoroacetamides.

We first tested the reaction of *N*-[2-bromomethyl(phenyl)]-trifluoroacetamide **11a** with methyl 1-phenylaziridine-2-carboxylate **12a** (Scheme 3). The reaction proceeded smoothly in refluxing acetonitrile. After consumption of starting materials

SCHEME 3. Reaction of *N*-[2-Bromomethyl(phenyl)]trifluoroacetamide 11a with Methyl 1-Phenylaziridine-2-carboxylate 12a

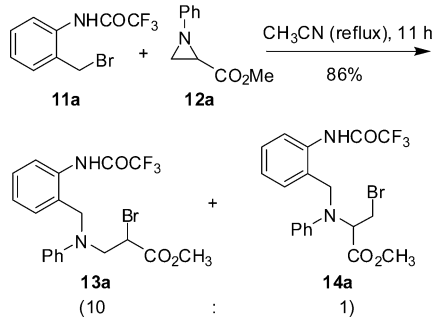
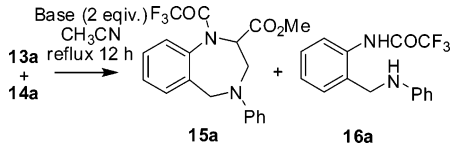


TABLE 1. Intramolecular Cyclization Reaction of 13a and 14a



	entry				
	1	2	3	4	5
base	NaOH	K_2CO_3	Cs_2CO_3	Et_3N	DABCO[b]
15a (%)[a]		31	65	80	
16a (%)[a]	82	47	21	7	73

[a] Isolated yield. [b] 1,4-Diazabicyclo[2.2.2]octane.

in 11 h, as monitored by TLC, the reaction was quenched and a mixture of ring- opening products **13a** and **14a** was isolated in 86% combined yield. The ratio of **13a** over **14a**, which was determined by ^{1}H NMR spectroscopy, was 10:1, indicating a highly regioselective attack of bromide to the C-2 position of the aziridine ring. It should be noted that, under the reaction conditions, viz. refluxing in acetonitrile, no intramolecular cyclization was observed. This was most probably due to the low nucleophilicity of the nitrogen atom of the trifluoroacetamide moiety. Elongating the reaction period to 24 h did not effect intramolecular cyclization either. Instead, the ratio of **13a** over **14a** was decreased from 10:1 to 6:1. The variation of the ratio **13a**:**14a** upon heating for a long period reflected that **13a** was able to transform into its thermodynamically more stable isomer **14a** via aziridinium intermediate **7**.

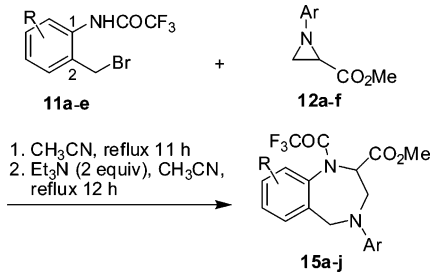
To facilitate the intramolecular nucleophilic displacement of bromide by amide, several bases were used to enhance the nucleophilicity of the nitrogen of trifluoroacetamide. As summarized in Table 1, the use of NaOH (2 equiv) did not lead to the desired cyclization reaction. On the contrary, the ring-opening products **13a**/**14a** underwent decomposition to give *N*-[2-anilinomethyl(phenyl)]trifluoroacetamide **16a** as the major product (entry 1, Table 1). Fortunately, K_2CO_3 assisted the cyclization reaction to afford 2-methoxycarbonyl-4-phenyl-1-trifluoroacetyl-1,4-benzodiazepine product **15a** in a moderate yield (entry 2, Table 1). The yield of **15a** was improved to 65% when Cs_2CO_3 was used as an inorganic base (entry 3, Table 1). While a strong organic base such as DABCO caused decomposition of **13a**/**14a** (entry 5, Table 1), triethylamine acted as an effective organic base to facilitate the formation of **15a** in high yield (entry 4, Table 1). It was noteworthy that, in all cases, no 3-methoxycarbonyl-4-phenyl-1-trifluoroacetyl-1,4-benzodiazepine isomer was found, suggesting that the intramolecular

(12) (a) For aziridinecarboxylate, see: Zhou, P.; Chen, B.-C.; Davis, F. A. Asymmetric syntheses with aziridinecarboxylate and aziridinephosphonate building blocks. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: New York, 2006; Chapter 3. (b) For a recent monograph, see: *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: New York, 2006. For recent reviews, see: (c) Osborn, H. M.; Sweeney, J. *Tetrahedron*: *Asymmetry* **1997**, *8*, 1693. (d) Xu, X. E. *Tetrahedron* **2004**, *60*, 2701.

(13) (a) Wang, J.-Y.; Wang, D.-X.; Zheng, Q.-Y.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2007**, *72*, 2040. (b) Wang, J.-Y.; Wang, D.-X.; Pan, J.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2007**, *72*, 9391.

(14) (a) D'hooghe, M.; De Kimpe, N. *Synlett* **2006**, 2089. (b) D'hooghe, M.; De Kimpe, N.; Van Speybroeck, V.; Waroquier, M.; De Kimper, N. *Chem. Commun*. **2006**, 1554. (c) Couturier, C.; Blanchet, J.; Schlama, T.; Zhu, J. *Org. Lett.* **2006**, *8*, 2183. (d) Kim, Y.; Ha, H.-J.; Han, K.; Ko, S. W.; Yun, H.; Yoon, H. J.; Kim, M. S.; Lee, W. K. *Tetrahedron Lett.* **2005**, *46*, 4407. (e) Lee, B. K.; Kim, M. S.; Hahm, H. S.; Kim, D. S.; Lee, W. K.; Ha, H.-J. *Tetrahedron* **2006**, *62*, 8393. (f) Denolf, B.; Mangelinkx, S.; Törnroos, K. W.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 3129.

TABLE 2. One-Pot Synthesis of 1,4-Benzodiazepine Derivatives 15a−j



entry	11	R	12	Ar	15	yield (%)[a]
1	**11a**	H	**12a**	C_6H_5	**15a**	65
2	**11a**	H	**12b**	4-F-C_6H_5	**15b**	71
3	**11a**	H	**12c**	4-Cl-C_6H_5	**15c**	54
4	**11a**	H	**12d**	4-Me-C_6H_5	**15d**	54
5	**11a**	H	**12e**	3-Me-C_6H_5	**15e**	49
6	**11a**	H	**12f**	4-MeO-C_6H_5	**15f**	53
7	**11b**	5-Cl	**12a**	C_6H_5	**15g**	53
8	**11c**	4-Cl	**12a**	C_6H_5	**15h**	48
9	**11d**	4-Me	**12a**	C_6H_5	**15i**	51
10	**11e**	3-Cl	**12a**	C_6H_5	**15j**	25

[a] Isolated yield.

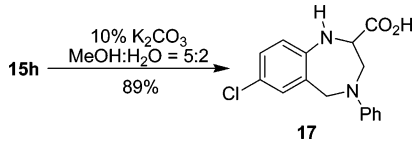
cyclization reaction did not occur with intermediate **14a**. This outcome might be rationalized most probably by the lower reactivity of nonactivated alkyl bromide within **14a** along with the low content of **14a** presented in an equilibrium with **15a** via aziridinium species.

Encouraged by the aforementioned results, we then attempted the one-pot synthesis of **15a** from the tandem ring-opening reaction of **12a** with **11a** followed, without isolation of intermediates **13a** and **14a**, by the Et_3N-mediated intramolecular cyclization reaction. Gratifyingly, the reaction proceeded effectively to furnish **15a** in good yield (entry 1, Table 2). To examine its scope and limitation, this one-pot synthesis of 1,4-benzodiazepine derivatives was further studied with a number of substituted *N*-[2-bromomethyl(phenyl)]trifluoroacetamides **11b−e** and methyl 1-arylaziridine-2-carboxylates **12b−f**. As demonstrated in Table 2, with the exception of **11e**, with a Cl atom at the meta position of the benzene ring, all substrates irrespective of the electronic nature of the substituents on both benzene rings underwent efficient tandem reaction to produce the corresponding 1,4-benzodiazepine products **15b−i** in moderate to good yields (entries 2 to 9, Table 2). The low chemical yield obtained for product **15j** was probably attributable to the steric hindrance of reactant **11e**. In other words, the 3-chloro substituent might pose an unfavorable steric effect on the reactivity of benzyl bromide.

All spectroscopic data and microanalysis results were in agreement with the structure of 1,4-benzodiazepine products. However, 2- and 3-methoxycarbonyl-1,4-benzodiazepines are not easily differentiated on the basis of spectra. To allow a definitive assignment of structure, X-ray crystallographic analysis was performed on **15e** (Figure S1, Supporting Information). It is interesting to note that the 1,4-benzodiazepine molecule adopts a boat conformation with the substituents on both nitrogen atoms being cis-oriented.

The reaction between *N*-[2-bromomethyl(phenyl)]trifluoroacetamides and methyl 1-arylaziridine-2-carboxylates not only provided a straightforward synthetic route to the 1,4-benzodiazepine core structure, but also generated a set of functionalized

SCHEME 4. Hydrolysis of Compound 15h



molecules that are not readily available by other synthetic methods. In addition, the products obtained from the current study are very useful for further chemical modification. When treated with K_2CO_3, for example, **15h** underwent efficient hydrolysis to afford **17** in 89% yield (Scheme 4). Synthesis of a 1,4-benzodiazepine library based on further functionalizations on the secondary amino group and carboxylic group of **17** is feasible.

In conclusion, we have established a new strategy for the synthesis of 1,4-benzodiazepine derivatives based on the interaction of methyl 1-arylaziridine-2-carboxylates with *N*-[2-bromomethyl(phenyl)]trifluoroacetamides. This one-pot synthesis proceeded via the *N*-benzylation and highly regioselective ring-opening reaction of aziridine by bromide anion followed by the Et_3N-mediated intramolecular cyclocondensation between amide nitrogen and alkyl bromide moieties. The easy availability of starting materials, simple and convenient synthetic procedure, and formation of functionalized 1,4-benzodiazepine scaffold ready for further chemical modifications render this method very useful in synthetic and medicinal chemistry.

Experimental Section

Ring-Opening Reaction of Methyl 1-Phenylaziridine-2-carboxylate 12a with *N*-(2-(Bromomethyl)phenyl)-2,2,2-trifluoroacetamide 11a. A mixture of methyl 1-phenylaziridine-2-carboxylate **12a** (1 mmol) and *N*-(2-(bromomethyl)phenyl)-2,2,2-trifluoroacetamide **11a** (1 mmol) in acetonitrile (10 mL) was refluxed for 11 h. After completion of the reaction, as monitored by TLC (ethyl acetate:petroleum ether = 1:8), the reaction mixture was cooled to room temperature and the solvent was removed under vacuum. The residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether and ethyl acetate (10:1) to give a mixture of **13a** and **14a**. Products **13a** and **14a** were not separable by column chromatography, but their ratio could be estimated satisfactorily from the ^{1}H NMR spectrum of the mixture.

Intramolecular Cyclization Reaction of 13a + 14a. A mixture of **13a** and **14a** (0.5 mmol) and base (0.6 mmol) (see Table 1) in acetonitrile (10 mL) was refluxed for 12 h until the starting **13a** and **14a** was consumed, which was monitored by TLC (ethyl acetate:petroleum ether = 1:8). After the reaction mixture was cooled to room temperature, the solvent was removed under vacuum. The product was extracted into ether, the organic phase was dried with anhydrous $MgSO_4$, and the solvent was evaporated in vacuo. The residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether and ethyl acetate (10:1) to give pure product **15a**.

General Procedure for Synthesis of 1,4-Benzodiazepine Derivatives 15 from the One-Pot Reaction of *N*-[2-Bromomethyl(phenyl)]trifluoroacetamides 11 and Methyl 1-Arylaziridine-2-carboxylates 12. A mixture of **11** (1mmol) and **12** (1 mmol) in acetonitrile (10 mL) was refluxed. After the starting materials were consumed (11 h), which was monitored by TLC (ethyl acetate: petroleum ether = 1:8), the mixture was cooled and triethylamine (1.2 mmol) was added. The resulting mixture was then refluxed for another 12 h. The solvent was removed under vacuum, and water (30 mL) was added. After extraction with diethyl ether (20 × 3 mL), the organic phase was dried with anhydrous

$MgSO_4$, and the solvent was removed under vacuum. The residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether and ethyl acetate (10:1) to give pure product **15**.

Hydrolysis of Compound 15h. A solution of **15h** (1 mmol) and K_2CO_3 (5 mmol) in a mixture of methanol and water (v:v = 5:2, 10 mL) was stirred for 2 days until the starting **15h** was consumed, which was monitored by TLC. After removal of the solvent under vacuum, the residue was chromatographed on a reverse-phase ODS column (35−70 μm) eluting with a mixture of water and methanol to give pure product **17** in 89% yield.

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Supporting Information Available: Full characterization of all products, ^1H and ^{13}C NMR spectra of products **15**, and X-ray single-crystal structure of **15e** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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