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Microwave- and Photoirradiation-Induced Staudinger Reactions of Cyclic Imines and Ketenes Generated from α-Diazoketones. A Further Investigation into the Stereochemical Process

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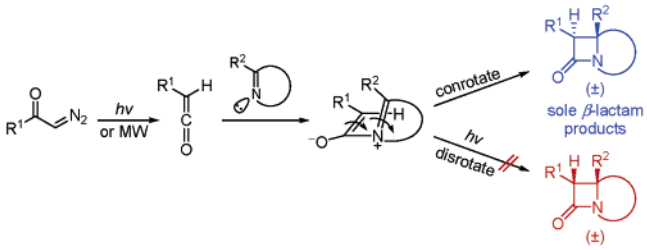

Reactions of ketenes generated from α-diazoketones with a series of acyclic and cyclic imines were investigated under both microwave and photoirradiation conditions. The results indicate that the zwitterionic azabutadiene-type intermediates yielded from imines and ketenes undergo a conrotatory ring closure exclusively to produce β-lactams. It is notable that no Woodward−Hoffmann product was found under the ultraviolet irradiation. The photoirradiation-induced Staudinger reaction shows a different stereoselectivity from the electrocyclic reaction of substituted 1,3-butadiene.

The β-lactam (2-azetidinone) skeleton is the key structural element of the most widely employed class of antibacterial agents, the β-lactam antibiotics.[1] The first β-lactam ring system was synthesized by H. Staudinger in 1907,[2] but β-lactams as a class of compounds became attractive only after it was established that penicillin contained a β-lactam unit as the structural feature.[3] Although many methods for the syntheses of β-lactam derivatives have been developed,[4] the Staudinger reaction, involving the [2 + 2] cycloaddition reaction of imines and ketenes, is regarded as one of the most versatile procedures for the stereocontrolled synthesis of 3,4-disubstituted 2-azetidinones (β-lactams).[5] Typically, ketenes are generated either from acid chlorides and related derivatives in the presence of tertiary amine thermally[6] or from metal carbenes photochemically.[7] Subsequent reactions with imines yield the desired β-lactams in a one-pot procedure.

In recent years, Podlech and co-workers introduced α-diazoketones derived from α-amino acids as precursors of ketenes into the microwave- and photoirradiation-induced Staudinger reaction and successfully prepared stereospecific β-lactams, *trans*-β-lactams, with different stereosubstitution.[8,9] Their relative configurations are different from the products of the common thermal-type Staudinger reaction. Although Podlech et al. tried to explain the difference and proposed a stereochemical process for their reaction,[8a,8d,9] no experimental evidence has been found to support the rationale until now. Moreover, a detailed investigation into the stereochemical process of the photoirradiation-induced Staudinger reaction has not been carried out. Herein, we report the microwave- and photoirradiation-assisted reactions of α-diazoketones with a series of acyclic and cyclic imines. These results experimentally prove the proposal of Podlech et al. and indicate that the zwitterionic azabutadiene-type intermediates generated in the photoirradiation-induced Staudinger reaction cannot undergo a disrotatory ring closure to form β-lactams. This is not in accordance with the stereochemistry of the electrocyclic reaction of substituted 1,3-butadiene.

In our previous papers, we synthesized a series of heterocycle-fused β-lactams under thermal conditions.[10] To further investigate the stereochemical process and to prepare the bicyclic β-lactams with different stereosubstitutions, we conducted the Staudinger reactions of α-diazoketone **1** with imines **2a**−**c**, **3a**−**d**, and **4a**,**b**, respectively, under microwave and photoirradiation conditions. With a series of acyclic imines **2a**−**c** (**2a** for *N*-aryl imine; **2b** for *N*-benzyl, nonconjugated imine; **2c** for *N*-alkyl and sterically hindered imine), *trans*-β-lactams **5a**−**c** were obtained exclusively under both conditions (Scheme 1 and Table 1, entries 1−3). Their

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(8) For photoirradiation-induced Staudinger reaction, see: (a) Podlech, J.; Linder, M. R. *J. Org. Chem.* **1997**, *62*, 5873−5883. (b) Linder, M. R.; Podlech, J. *Org. Lett.* **1999**, *1*, 869−871. (c) Maier, T. C.; Frey, W. U.; Podlech, J. *Eur. J. Org. Chem.* **2002**, 2686−2689. (d) Linder, M. R.; Frey, W. U.; Podlech, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2566−2577.

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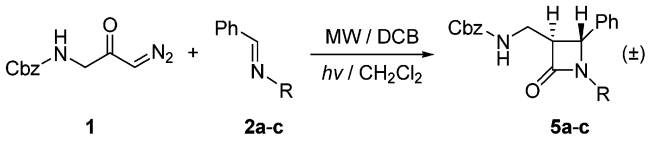
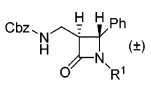
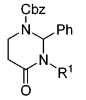
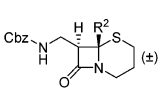
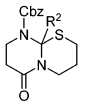
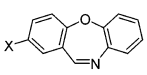
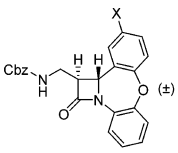
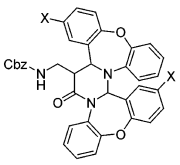
SCHEME 1. Reactions of Acyclic Imines and α-Diazoketone 1



1 **2a-c** **5a-c**

MW = microwave, *hv* = photoirradiation, DCB = 1,2-dichlorobenzene

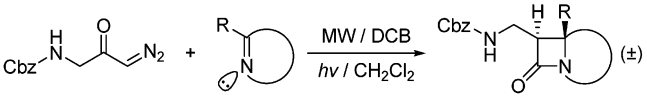
TABLE 1. Products of Microwave- and Photoirradiation-Induced Reactions

Entry	Imine	β-Lactam (%) MW	β-Lactam (%) *hv*	Byproduct (%) (*hv* only)
				
1	**2a** R^1 = Ph	**5a** (29)	**5a** (38)	**8** (9)
2	**2b** R^1 = Bn	**5b** (57)	**5b** (70)	—
3	**2c** R^1 = *t*-Bu	**5c** (28)	**5c** (64)	—
				
4	**3a** R^2 = Ph	**6a** (35)	—	**9a** (8)
5	**3b** R^2 = *p*-MeOPh	**6b** (27)	—	**9b** (10)
6	**3c** R^2 = *p*-MePh	**6c** (30)	—	**9c** (9)
7	**3d** R^2 = *p*-ClPh	**6d** (40)	—	**9d** (7)
				
8	**4a** X = H	**7a** (71)	**7a** (29)	**10a** (21)
9	**4b** X = Me	**7b** (55)	**7b** (21)	**10b** (23)

relative configurations were determined by the coupling constants between the protons at C-3 and C-4 ($J_{H(C3)-H(C4)}$ = 1.5 ∼ 2.4 Hz). This is in agreement with the results of Podlech et al.[8,9] However, when a series of cyclic imines, including 2-substituted pyrrolines, oxazolines, 5,6-dihydro-4*H*-1,3-oxazine, and thiazoline, were attempted in the reactions with α-diazoketones under the same conditions, no β-lactam derivative was generated.[11] Another type of cyclic imines, 2-aryl-5,6-dihydro-4*H*-1,3-thiazines **3a**−**d**, were further attempted, and bicyclic β-lactams **6a**−**d** were obtained under the microwave irradiation (Scheme 2 and Table 1, entries 4−7). To our surprise, in their photochemical reactions, no β-lactam was formed and only byproducts **9a**−**d** were separated (Table 1, entries 4−7, the last column). This promoted us to consider the stability of dihydrothiazine-fused β-lactam derivatives under photoirradiation. To confirm our consideration, 20 mg of β-lactam **6a** was irradiated under photoirradiation conditions, and it was found that β-lactam **6a** had

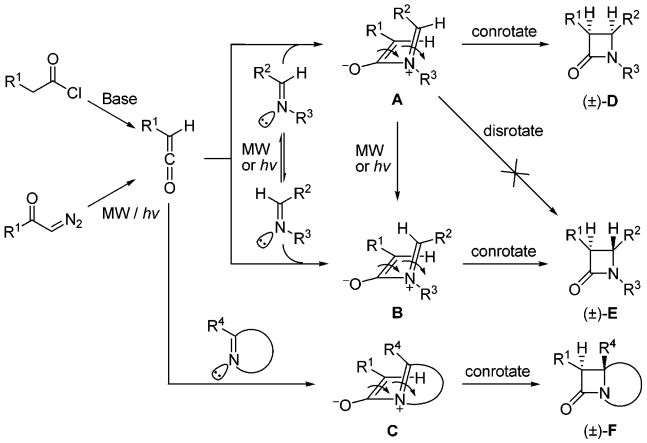
(11) The following cyclic imines, including 2-cyclohexyl-1-pyrroline, 2-phenyl-1-pyrroline, 2-methyloxazoline, 2-phenyloxazoline, 2-(4-chlorophenyl)oxazoline, 5,6-dihydro-2-phenyl-4*H*-1,3-oxazine, and 2-phenylthiazoline, and α-diazoketones, such as 2-diazo-1-phenylethanone, 1-diazo-3-phenyl-2-propanone, were also attempted. However, no good result was obtained.

SCHEME 2. Reactions of Cyclic Imines and α-Diazoketone 1



1 **3a-d, 4a-b** **6a-d, 7a-b**

SCHEME 3. Mechanism of the Staudinger Reactions



completely decomposed to an inseparable mixtrue. This seemed to be the reason no bicyclic β-lactam derivative of the thiazines **3** was obtained in the photoirradiation-induced Staudinger reaction.

To further investigate the reactions, we designed and prepared cyclic imines **4a**−**b**, substituted dibenzo[*b*,*f*][1,4]-oxazepines, which have a similar structural feature to the acyclic imine **2a**. Fortunately, bicyclic β-lactams **7a**,**b** were obtained from the reaction of imines **4a**,**b** and α-diazoketone **1** stereospecifically under both microwave and photoirradiation conditions (Scheme 2 and Table 1, entries 8 and 9). In the photochemical reaction, byproducts **10a**,**b** of [2 + 2 + 2] cyclization were also obtained and identified, which are similar to the product generated from the reaction of 3,4-dihydroisoquinoline and Cbz-Ala-CHN_2 reported previously.[8d] However, no similar byproduct was found under microwave conditions.

The mechanism of the Staudinger reaction under thermal conditions has been investigated in detail,[6c,12,13] and the most widely accepted mechanism could be described as follows: A ketene that is usually generated by the elimination of hydrogen chloride from an acyl chloride is attacked by the lone pair of the nitrogen atom in an (*E*)-imine to form an intermediate **A**. The zwitterionic intermediate **A** subsequently undergoes a conrotatory ring closure to form a *cis*-β-lactam **D** (Scheme 3). However, Podlech et al. found that a *trans*-β-lactam **E** was formed exclusively from the reaction of an α-diazoketone and an (*E*)-imine under both microwave and

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photoirradiation conditions. They proposed that the formation of the *trans*-β-lactam **E** in the photochemical reaction is as follows (Scheme 3):[8a,8d] a diazoketone undergoes a Wolff rearrangement to yield a ketene under photoirradiation that is attacked by the lone pair of the nitrogen atom in the (*E*)-imine to form the intermediate **A**. The weakening of the C=N double bond in the intermediate **A** could allow for a rotation to a less hindered intermediate **B** due to the photochemical excitation. It is also possible that the intermediate **B** is formed from the ketene and a (*Z*)-imine generated from the photoirradiation-induced isomerization of the (*E*)-imine. The intermediate **B** subsequently leads to the *trans*-β-lactam **E** after a conrotatory ring closure (with some question marks in their proposed scheme[8a,8d]). In a similar mode, they assumed that the formation of *trans*-β-lactams in the microwave-assisted reaction was due to the thermal isomerization of the imine moiety.[9]

To support the proposed mechanism, Podlech and coworkers investigated the reactions by employing *N*-*tert*-butyl imines. The use of a more hindered R^3 group on the nitrogen atom (e.g., $R^3 = t$-Bu) would discourage the *E* to *Z* isomerization of the imine. Thus, it is expected that when *N*-*tert*-butyl imines were employed in photochemical Staudinger reactions, the products (thought to be *cis*-β-lactams or a mixture of *trans*- and *cis*-β-lactams) might be different from the reactions involving less hindered imines. This means, if *cis*-β-lactams are obtained in such photochemical reactions, the proposal of the *E* to *Z* isomerization of the imine moiety could be supported experimentally. In fact, even with *N*-*tert*-butylmesitylenecarbaldimine, again exclusively *trans*-configured β-lactams were obtained.[8d] We also investigated the reaction of *N*-*tert*-butyl imine **2c** with diazoketone **1** and found that *trans*-β-lactam **5c** was exclusively obtained under both conditions. These facts obviously indicate that the use of a *tert*-butyl group as R^3 on the nitrogen atom is not suitable for verifying the *E* to *Z* isomerization of the imine moiety.

It is well-known that (*Z*,*Z*)-2,4-hexadiene undergoes a conrotatory ring closure to produce *trans*-3,4-dimethylcyclobutene under thermal conditions and undergoes a disrotatory ring closure to form *cis*-3,4-dimethylcyclobutene under photochemical conditions according to the Woodward−Hoffmann rule.[14] As the intermediate **A** could be considered as a substituted azabutadiene, is it possible that the intermediate **A** undergoes a disrotatory ring closure to generate the β-lactam **E** under the ultraviolet irradiation as (*Z*,*Z*)-2,4-hexadiene? Podlech and co-workers did not mention this possible pathway. Although they attempted to prove their proposed mechanism by using some cyclic imines in photochemical reactions, they did not observe the formation of bicyclic β-lactams. Thus, they suggested that the activation energies of the ring-closure of certain cyclic zwitterionic intermediates were higher (12 kJ/mol) than those of acyclic zwitterionic intermediates after calculations with semiempirical methods.[8d] The rationale for the stereochemical process in the reaction is still in doubt due to the absence of experimental evidence.

In comparison with acyclic imines, cyclic imines are more rigid. When they react with ketenes to give rise to bicyclic β-lactams, the isomerization of the imine moiety cannot occur. So they can be used as a probe to the isomerization. Determining the relative configurations of the bicyclic β-lactams obtained in the microwave- and photoirradiation-induced Staudinger reactions allowed the stereochemical process to be understood more clearly. On the basis of our results, bicyclic β-lactams **6a**−**d** and **7a**,**b**, with the relative configurations described as β-lactams **F** (Scheme 3), were obtained from the reaction of cyclic imines with the ketene. Their relative configurations were determined by the XRD analysis of product **6a** and the NMR analysis (the coupling constant of the protons on C-3 and C-4 is 1.4 Hz for product **7a**). The results indicate that intermediates **C**, generated under both microwave and photoirradiation conditions, undergo a conrotatory ring closure exclusively to yield β-lactams **F**. What is important is that the zwitterionic azabutadiene-type intermediate **C** is a 4π-electron system, but it cannot undergo a disrotatory ring closure to form a β-lactam under the ultraviolet irradiation. This is quite different from the stereochemistry of the electrocyclic reaction of substituted 1,3-butadiene. That is to say, the photoirradiation-induced Staudinger reaction does not obey the Woodward−Hoffmann rule. Meanwhile, these results provide direct experimental evidence for the proposal of Podlech et al. Now we can confirm that the formation of β-lactams **E** from acyclic imines and ketenes indeed involves the *E* to *Z* isomerization of the imine moiety, even when there is a bulky group (such as *tert*-butyl) on the nitrogen atom of the imine. We propose that the *E* to *Z* isomerization occurs most likely in the intermediate **A** rather than in the imine itself, because the C=N double bond in the zwitterionic intermediate **A** is weaker (lower bond order) than that in the imine and the intermediate **B** is much less sterically hindered than the intermediate **A**.

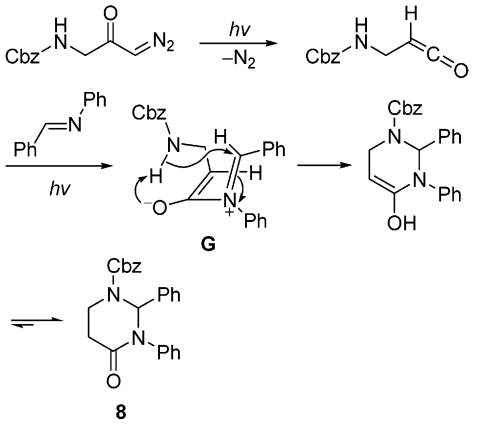
Why does the azabutadiene-type intermediate show a different stereochemical process from substituted 1,3-butadiene under photochemical conditions? The theoretical studies of Cossio et al. showed that the dihedral angle, formed by the two double bonds in the zwitterionic intermediate **A**, could vary from ca. 40−180°.[13b] This means that the two double bonds are not coplanar, which may cause difficulty in a disrotatory ring closure due to the least-motion-principle.[8d] Both theoretical and experimental results demonstrate that a conrotatory ring closure occurs exclusively and the two-step mechanism is also suitable for the microwave- and photoirradiation-assisted Staudinger reactions. We can conclude that the zwitterionic intermediates in the Staudinger reactions can only undergo a conrotatory ring closure to produce β-lactam derivatives.

It is interesting that byproducts **8** and **9a**−**d** were separated from the reaction of α-diazoketone **1** with imines **2a** and **3a**−**d**, respectively, under photochemical conditions. They are presumed to be formed via an intramolecular six-membered ring transition state (Scheme 4). However, it is unclear whether the process is stepwise or concerted.

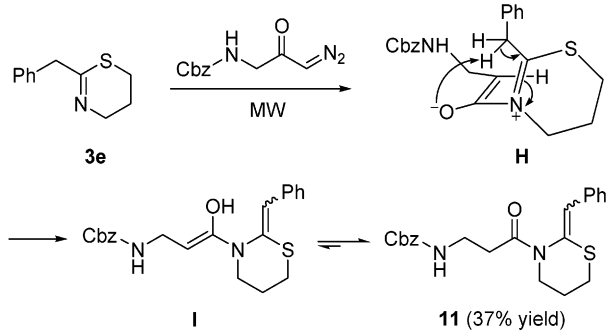
Moreover, the reaction of 2-benzyl-5,6-dihydro-4*H*-1,3-thiazine **3e** and α-diazoketone **1** was also conducted

(14) Solomons, T. W. G. *Organic Chemistry*, 4th ed.; John Wiley & Sons, Inc.: New York, 1988; p 1164.

SCHEME 4. Proposed Mechanism for the Formation of 1-Benzyloxycarbonyl-2,3-diphenyltetrahydropyrimidin-4(1*H*)-one (8)



SCHEME 5. Proposed Mechanism for the Formation of 3-(3-Benzyloxycarbonylaminopropionyl)-2-benzylidene-1,3-thiazacyclohexane (11)



under microwave conditions. It is strange that byproduct **11** was formed in moderate yield instead of the desired β-lactam. Its formation is proposed as follows: an intermediate **H**, generated from the attack of imine **3e** to the ketene, undergoes a proton transfer to yield an enol intermediate **I** through an intramolecular six-membered ring transition state due to the existence of the more acidic benzylic hydrogen atom adjacent to an imine bond. The intermediate **I** tautomerizes into ketone derivative **11** (Scheme 5). It is also unclear whether the process is stepwise or concerted.

It seems reasonable that favorable conformations, which are formed due to the existence of certain dihedral angles in the intermediates **G** and **H**, geometrically promote the formation of byproducts **8**, **9a**−**d**, and **11** via intramolecular reactions.

In conclusion, reactions of ketenes with acyclic and cyclic imines were investigated under microwave and photoirradiation conditions. The results indicate that the zwitterionic azabutadiene-type intermediates generated from imines and ketenes only undergo a *conrotatory* ring closure to produce β-lactams. This reveals the inapplicability of the Woodward−Hoffmann rule to the photoirradiation-induced Staudinger reaction. Second, when acyclic imines are employed, the *E* to *Z* isomerization of the imine moiety in the zwitterionic intermediates induced by the microwave or ultraviolet irradiation will occur. Furthermore, our results provide direct experimental evidence for the proposed stereochemical process of the microwave- and photoirradiation-induced Staudinger reactions. Finally, on the basis of our results and the results of Podlech et al.,[9] the microwave-assisted Staudinger reaction can produce β-lactams with the same stereosubstitution as the photoirradiation-induced Staudinger reaction. The photochemical reaction often produces β-lactams with byproducts and sometimes is even inapplicable to the synthesis of some bicyclic β-lactams, while the microwave-assisted reaction is more efficient, convenient, and practical. Thus, the microwave-induced Staudinger reaction is a suitable method for the synthesis of bicyclic β-lactams.

Experimental Section

General Procedure for Microwave-Assisted Reaction of α-Diazoketone and Imines. Cbz−Gly−CHN_2 **1** (233 mg, 1.00 mmol) and imine (2 mmol) were dissolved in 15 mL of dry 1,2-dichlorobenzene. The solution was irradiated by microwave for 2−3 min under a nitrogen atmosphere until it refluxed. After cooling, the resulting mixture was separated directly on a silica gel column (30 g of silica gel) with a mixture of petroleum ether (60−90 °C) and ethyl acetate (5:1 to 3:1, v/v) as an eluent to afford corresponding products.

General Procedure for Photochemical Reaction of α-Diazoketone and Imines. A solution of Cbz−Gly−CHN_2 **1** (233 mg, 1.00 mmol) and imine (2 mmol) in 15 mL of dry CH_2Cl_2 was stirred and irradiated by the high−pressure mercury lamp under a nitrogen atmosphere at −20 °C for 1 h. The solution was concentrated, and the residue was separated on a silica gel column (30 g of silica gel) with a mixture of petroleum ether (60−90 °C) and ethyl acetate (5:1 to 3:1, v/v) as an eluent to afford corresponding products.

(±)-*cis*-8-Benzyloxycarbonylaminomethyl-1-phenyl-2-thia-6-aza-bicyclo[4.2.0]octan-7-one (6a). White solid; mp 150−151 °C. ^{1}H NMR (300 MHz): δ 1.81 (m, 2H), 2.60 (m, 2H), 3.04 (m, 3H), 3.71 (t, J = 7.8 Hz, 1H), 4.11 (m, 1H), 4.84 (s, br, 1H), 5.00 (s, 2H), 7.31−7.54 (m, 10H). ^{13}C NMR (75.5 MHz): δ 23.6, 25.3, 37.5, 37.7, 64.1, 65.5, 66.5, 127.4, 127.9, 128.3, 128.4, 128.6, 136.2, 136.8, 155.7, 166.3. MS (EI) *m/z*: 382 (M^+, 1.0),354 (M^+ − CO, 1.9), 291 (M^+ − Bn, 5.6), 218 (M^+ − $CbzNHCH_2$, 100). IR υ (cm^{-1}): 1751, 1707. Anal. Calcd for $C_{21}H_{22}N_2O_3S$: 382.1351. Found: 382.1358.

(±)-*trans*-2-Benzyloxycarbonylaminomethyl-azeto[1,2-*d*]dibenzo[*b*,*f*]oxazepin-1-one (7a). Pale yellow oil. ^{1}H NMR (400 MHz): δ 3.77 (m, 2H), 3.86 (m, 1H), 5.10 (s, 2H), 5.49 (d, J = 1.4 Hz, 1H), 5.58 (s, br, 1H), 6.98−7.03 (m, 2H), 7.19−7.24 (m, 4H), 7.27−7.31 (m, 6H), 7.93−7.94 (m, 1H). ^{13}C NMR (75.5 MHz): δ 38.9, 54.1, 56.0, 67.0, 119.9, 121.5, 121.6, 124.5, 125.1, 125.3, 126.0, 128.0, 128.1, 128.5, 129.7, 130.1, 130.2, 136.2, 143.9, 156.7, 158.2, 163.8. MS (EI) *m/z*: 400 (M^+, 5.0), 382 (M^+ − H_2O, 100), 309 (M^+ − Bn, 53), 292 (M^+ − BnOH, 14), 236 (M^+ − $CbzNHCH_2$, 32.6). IR υ (cm^{-1}): 1748, 1717. Anal. Calcd for $C_{24}H_{20}N_2O_4$: 400.1423. Found: 400.1422.

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Supporting Information Available: Experimental details and spectroscopic data for compounds **5a**−**c**, **6b**−**d**, **7b**, **8**, **9a**−**d**, **10a**,**b**, and **11**, ^{1}H NMR and ^{13}C NMR spectra of all unknown compounds **5a**−**c**, **6a**−**d**, **7a**,**b**, **8**, **9a**−**d**, **10a**,**b**, and **11**, DEPT spectra of compounds **7a**, **9a**, and **10a**, gHSQC spectra of compounds **7a** and **9a**, and the crystal structure of **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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