# Regiochemical Studies of the Ring Expansion Reactions of Hydroxy Azides with Cyclic Ketones

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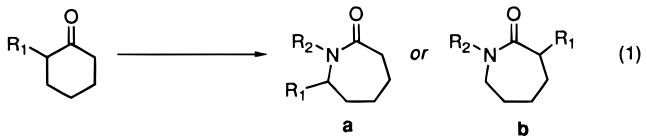
The regiochemistry of ring expansions of 2-substituted cyclic ketones using 1,2-azidoethanol and 1,3-azidopropanol was examined. It was determined that the reactions of ketones with an adjacent methyl or ethyl group are generally unselective, but that bulkier substituents lead to preferential migration of the more highly substituted carbon. In addition, it was found that ketones bearing inductively electron-withdrawing substituents (OMe, Ph, Br) undergo selective migration of the less highly substituted carbon. For some substrates, alternative reaction pathways were also identified.

Nitrogen ring expansion reactions are capable of converting an unsymmetrically substituted ketone to one of two regioisomeric lactams (eq 1). In general, the Schmidt and Beckmann reactions preferentially lead to products of the type **a** ($R_2$ = H), in which the most highly substituted carbon has undergone migration to an electron-deficient nitrogen atom.[1] On the other hand, the only ring-expansion technique that reliably affords products of the type **b** (where $R_2$ = alkyl) utilizes the photochemical rearrangement of an intermediate oxaziridine.[2]




(1)

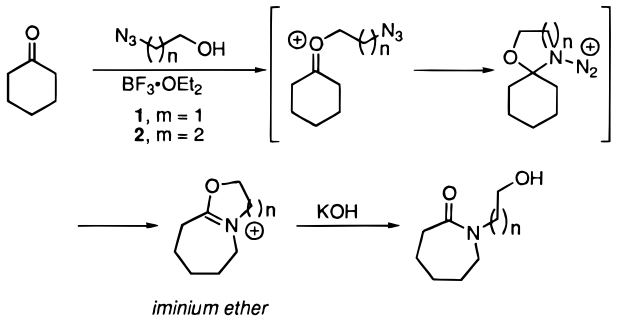
The direct synthesis of *N*-substituted lactams from ketones can also be carried out using a hydroxy azide, such as **1** or **2**, as the nitrogen atom source.[3] This process involves the Lewis acid-promoted formation of an *N*-diazonium intermediate, which undergoes rearrangement to give an iminium ether intermediate that can be hydrolyzed by base (Scheme 1). In this paper, the regiochemistry of this process is examined using a series of differentially 2-substituted cyclopentanones and cyclohexanones as prototypical examples.

## Results and Discussion

A series of 2-substituted cyclohexanones and cyclopentanones was examined (Table 1). The α-substituent was systematically varied to include increasingly bulky alkyl (Me, Et, *i*-Pr, *t*-Bu) and inductively electron-withdrawing substituents (Ph, OMe, Br). In addition, azido alcohols containing two or three carbons were used. All starting materials were purchased or synthesized according to literature methods (see Experimental Section). Each of the reactions was carried out according to the previously reported standard protocol, in which 2 equiv of $BF_3$•$OEt_2$ was added to a solution of 1.5 equiv of azido alcohol **1** or **2** and the ketone (1 equiv) in $CH_2Cl_2$ at −0 °C. The reactions were allowed to come to room temperature and then heated to reflux for 2 days. In both examples bearing 2-bromo substitution, the reactions were carried out at room temperature. At the end of the reaction period, the iminium ether products were hydrolyzed by treatment with 15% aq KOH for ca. 1 h. The ratios of lactams thus obtained were usually determined by $^1$H NMR examination of the crude reaction mixture, although in some cases the ratios were obtained from the weights of the isolated isomers. In general, the isomers were separable by column chromatography. In most cases, the structures of the regiosomers could be determined using $^1$H NMR, recognizing that the products resulting from migration of the less highly substituted carbon **3a**−**r** are expected to have one more downfield (>3.0 ppm) resonance when compared to their counterparts **4a**−**r**. In some cases, it was thought prudent to more thoroughly analyze the spectra through 2-D NMR techniques. Each regioisomeric assignment is detailed in the Supporting Information.

In several examples, side products resulting from idiosyncratic reaction pathways complicated the analysis of regioselectivity (Scheme 2). In the reaction involving

**Scheme 1**

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(1) (a) Gawley, R. E. *Org. React.* **1988**, *35*, 1−420. (b) Wolff, H. *Org. React.* **1946**, *3*, 307−336. (c) Smith, P. A. S. In *Molecular Rearrangements*; de Mayo, P., Ed.; John Wiley & Sons: New York, 1963; Vol. 1, pp 457−591. (d) Nitrogen ring-expansion reactions of bicyclic ketones are known to depend strongly on substitution type: Krow, G. R. *Tetrahedron* **1981**, *37*, 1283−1307.

(2) (a) Oliveros-Desherces, E.; Rivière, M.; Parello, J.; Lattes, A. *Tetrahedron Lett.* **1975**, 851−854. (b) Aubé, J.; Hammond, M.; Gherardini, E.; Takusagawa, F. *J. Org. Chem.* **1991**, *56*, 499−508. Correction: *Idem. Ibid. J. Org. Chem.* **1991**, *56*, 4086.

(3) (a) Gracias, V.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 8047−8048. (b) Gracias, V.; Frank, K. E.; Milligan, G. L.; Aubé, J. *Tetrahedron* **1997**, *53*, 16241−16252. (c) Forsee, J. E.; Smith, B. T.; Frank, K. E.; Aubé, J. *Synlett* **1998**, 1258−1260. (d) Furness, K.; Aubé, J. *Org. Lett.* **1999**, *1*, 495−497. (e) Forsee, J. E.; Aubé, J. *J. Org. Chem.* **1999**, *64*, 4381−4385.

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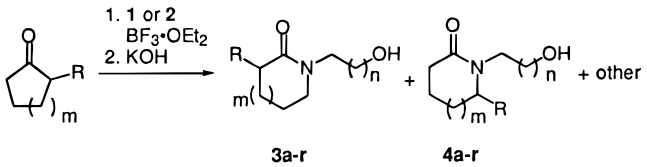
**Table 1. Regioselectivity in Lewis Acid-Promoted Reactions of Cyclic Ketones with Azido Alcohols**

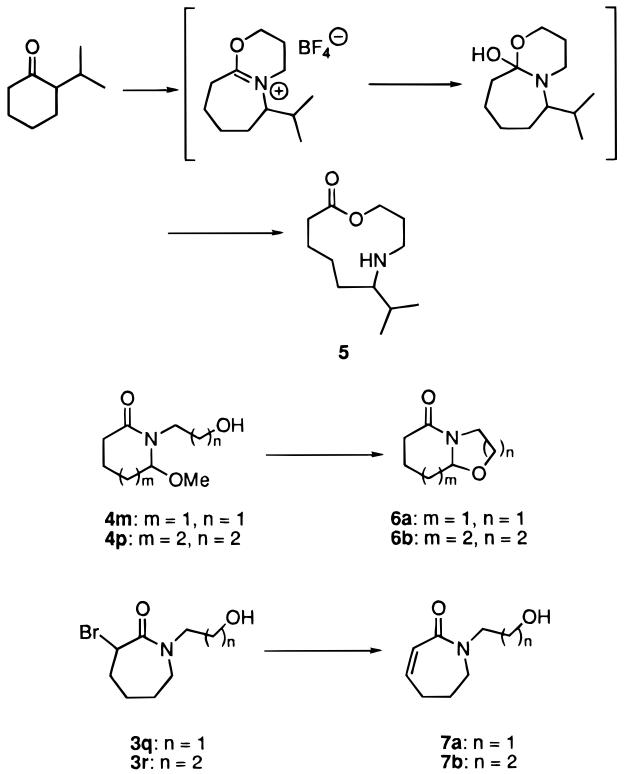



**3a-r** **4a-r**

| entry | compd | R | azide | m | n | yield (%) | ratio **3:4:**other[a] |
|---|---|---|---|---|---|---|---|
| 1 | **a** | Me | **1** | 1 | 1 | 89 | 53:47 |
| 2 | **b** | Me | **2** | 1 | 2 | 86 | 88:12 |
| 3 | **c** | Me | **1** | 2 | 1 | 83 | 45:55 |
| 4 | **d** | Me | **2** | 2 | 2 | 95 | 55:45 |
| 5 | **e** | Et | **1** | 2 | 1 | 85 | 42:58 |
| 6 | **f** | Et | **2** | 2 | 2 | 94 | 57:43 |
| 7 | **g** | *i*-Pr | **1** | 2 | 1 | 80 | 21:79 |
| 8 | **h** | *i*-Pr | **2** | 2 | 2 | 40 | 23:54:23[b] (23:77) |
| 9 | **i** | *t*-Bu | **1** | 2 | 1 | 11 | 13:87 |
| 10 | **j** | *t*-Bu | **2** | 2 | 2 | NR | |
| 11 | **k** | Ph | **1** | 2 | 1 | 93 | 47:53 |
| 12 | **l** | Ph | **2** | 2 | 2 | 92 | >95:5 |
| 13 | **m** | OMe | **1** | 1 | 1 | 53 | 47:36:17[c] (47:53) |
| 14 | **n** | OMe | **2** | 1 | 2 | 76 | 91:9 |
| 15 | **o** | OMe | **1** | 2 | 1 | 52 | 91:9 |
| 16 | **p** | OMe | **2** | 2 | 2 | 68 | 90:0:10[d] (90:10) |
| 17 | **q** | Br | **1** | 2 | 1 | 58 | 76:0:24[e] (>95:5) |
| 18 | **r** | Br | **2** | 2 | 2 | 51 | 83:0:17[f] (>95:5) |

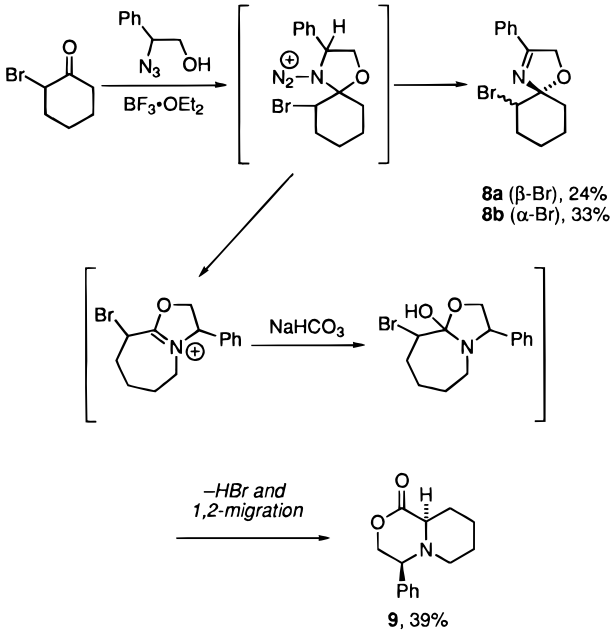
[a] In cases where side products were isolated, the effective regioselectivity (**3:4**) is indicated in parentheses. The identity of each side product is indicated in Scheme 2. [b]Lactone **5**. [c]Bicyclic lactam **6a**. [d]Bicyclic lactam **6b**. [e]α,β-Unsaturated lactam **7a**. [f]α,β-Unsaturated lactam **7b**.

**Scheme 2**




2-isopropylcyclohexanone, regioisomer **4h** (migration of the more highly substituted carbon) was accompanied by lactone **5** ($\nu_{C=O} = 1740\ cm^{-1}$) resulting from the pathway shown in Scheme 2. Such products have been previously observed to arise from iminium ethers derived from macrocyclic lactones.[3c,e] Two products containing a mixed aminal linkage, **4m** and **4p**, apparently undergo cyclization with the side chain hydroxyl group to afford bicyclic products **6a** and **6b**, respectively. Finally, two α-bromo lactams (**3q** and **3r**) underwent dehydrohalogenation to afford the unsaturated lactams indicated. To focus attention on the regiochemical issues, the overall regioselectivity of each reaction that gave an additional side product is indicated in parentheses in Table 1.

**Scheme 3**




The combination of 2-bromocyclohexanone with a single example of a substituted hydroxy azide yielded interesting results (Scheme 3). Of the three products isolated from this reaction, none resulted from a simple ring-expansion pathway. The predominant course of the reaction provided two epimeric spiro compounds containing a 4*H*-oxazoline unit, apparently the result of hydride migration from the benzylic position of the *N*-diazonium species initially formed. Alternatively, a concerted elimination of $N_2$ and $H^+$ cannot be ruled out. The structures of both products were apparent from spectral analysis, but the stereostructure of **8a** was additionally secured through X-ray crystallography (Supporting Information). In addition, α-amino lactone **9** was obtained as a minor product. Such materials have been previously noted to occur in simpler systems, and are generally preferred using the $NaHCO_3$ conditions used in this specific experiment (inferior yields of the same products were obtained when KOH was used in the workup or if base was omitted altogether).[3c,e] Interestingly, only a single diastereomer of **9** (structure determined by X-ray; see Supporting Information) was obtained in these reactions, which used racemic ketone and hydroxy azide. However, this point was not pursued, and the yields were sufficiently low as to make stereochemical speculations based on this evidence imprudent.

The overall yields of the reactions were generally high throughout, although an understandable drop occurred with the very sterically crowded 2-*tert*-butylcyclohexanone. In the present work, superior results were obtained through the simple expedient of carrying out the

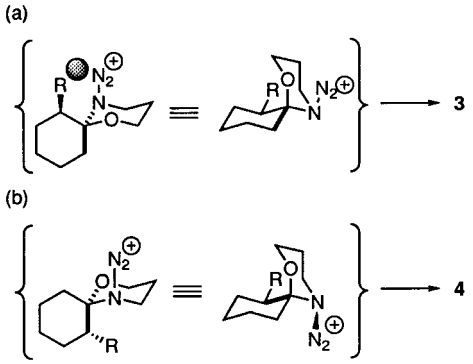



**Figure 1.** Comparison of transition structures resulting from equatorial addition of azide to the intermediate oxonium species, with the migrating bond shown in bold. The structures differ in the position of the diazonium moiety, which is (a) syn or (b) anti to the more highly substituted carbon.

reactions at reflux in $CH_2Cl_2$ (as opposed to the room temperature conditions previously reported[3]). The regiochemical outcomes seem to depend on two factors. First, the reactions are poorly selective when smaller alkyl groups (Me, Et) are used, although selectivity for migration of the more highly substituted carbon (i.e., products of the type **4**) was observed with increasing steric bulk of the 2-substituent. Second, the use of substituents with $\sigma$ electron-withdrawing character (Ph, OMe, and Br) significantly favored the opposite regioisomers **3**, in which the less highly substituted carbon becomes attached to nitrogen. The results are complicated by differences in ring size and hydroxy azide tether lengths (cf. entries 1 vs 2, 2 vs 4, 11 vs 12, and 13 vs 14). Clearly, changes in structure, and presumably conformation, are able to modify the overall trends in sometimes unpredictable ways, but the above generalizations seem to be valid nonetheless.

The effect of substituent size probably reflects differences in nonbonded interactions in the spirocyclic *N*-diazonium intermediates (Figure 1). In general, the preferential migration of a bond antiperiplanar to the leaving group has been presumed in the classical Schmidt and Beckmann reactions.[1] This supposition is also consistent with high stereoselectivity observed in the asymmetric ring-expansion reactions of hydroxy azides as reported elsewhere.[3a,d] The hydroxy azide can attack the intermediate oxonium ion from either an equatorial or an axial direction; again, previous work has indicated that the former is likely preferred[3a,d] although this point has not been rigorously proven. One possible explanation for the effect of increasing steric bulk of the 2-substituent on regiochemistry is that the alkyl group and the $N_2^+$ moieties experience various degrees of steric interaction when they are in a syn orientation. This orientation leads to migration of the less highly substituted carbon, affording **3**, as shown in Figure 1a. Conversely, the alternative arrangement in which the leaving group and the more highly substituted carbon are anti leads to migration of the more highly substituted carbon and gives compounds in series **4**. Since the diazonium ion is a small, cylindrical group, there is not much energy difference between these forms for small alkyl groups, and a preference only emerges for larger R groups.

The observed selectivity for compounds **3** in the case of ketones containing polar groups is very valuable because this mode of migratory selectivity is rarely observed in the classical Schmidt or Beckmann reactions (although a significant amount of methylene migration has been reported for the Schmidt or Baeyer−Villiger reactions of 2-halocyclohexanones[4]). It seems unlikely that a strictly steric interpretation of these results will suffice, inasmuch as there are no trends within this series that reflect substituent size alone. One possible explanation is that the electron-withdrawing substituent simply slows down migration of that group. Besides leading to the regiochemical results observed, this is also consistent with the result shown in Scheme 3. In this case, the simultaneous electronic deactivation of the more highly substituted carbon by bromine combined with activation of the benzylic position for hydride migration (which would leave behind a stabilized cation) led to the high proportion of compounds **8a**,**b**. This interpretation is supported by the fact that such products were *not* observed in reactions of 2-phenylazidoethanol with cyclohexanones lacking adjacent substitution.[3a] A similar argument has been made to explain the nearly exclusive methylene migrations observed in the acid-promoted ring-expansion reactions of 2-bromocyclohexanone with ethyl diazoacetate.[5]

In summary, the regiochemistry of the reaction of cyclic ketones with hydroxy azides under Lewis acids conditions has been investigated. Although fairly small α-alkyl substituents give essentially equal mixtures of regioisomers, larger groups favor migration of the more heavily substituted α-carbon and inductively electron-poor groups, regardless of size, favor migration of the less-substituted group.

## Experimental Section

**General methods** have been previously reported.[3b] All ketones have been purchased or prepared via the following reported procedures: **1** and **2**,[6] 2-ethylcyclohexanone,[7] 2-isopropylcyclohexanone,[8] 2-methoxycyclopentanone,[7] and 2-bromocyclohexanone.[9]

**General Procedure for the Synthesis of *N*-Hydroxyalkyl Lactams Using $BF_3{\cdot}OEt_2$. Reaction of 2-Methylcyclopentanone with Azido Alcohol 2: *N*-Hydroxyethyl-3-methylvalerolactam (3b) and *N*-Hydroxyethyl-6-methylvalerolactam (4b).** A solution of ketone (0.263 g, 2.307 mmol) and azido alcohol **2** (0.466 g, 4.614 mmol) in 8 mL of $CH_2Cl_2$ was cooled to 0 °C. $BF_3{\cdot}OEt_2$ (0.8 mL, 6.256 mmol) was added dropwise over 5 min; gas evolution was observed. The reaction was kept at 0 °C for 30 min, allowed to warm to room temperature, and then heated to reflux for another 24−48 h. The solution was concentrated, and 15% KOH was added to the residual oil. The reaction mixture was stirred for 1 h at room temperature. Additional $CH_2Cl_2$ was added, and the organic layer was dried (anhydrous $Na_2SO_4$), filtered, and concentrated to afford crude product, which was purified by column chromatography.

***N*-Hydroxypropyl-3-methylvalerolactam (3b)**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.23 (d, $J$ = 7.2 Hz, 3H), 1.54 (m, 1H), 1.72 (p, $J$ = 12.1, 5.9 Hz, 2H), 1.78 (m, 1H), 1.88−1.99 (m, 2H), 2.42 (s, $J$ = 14.2, 7.4 Hz, 1H), 3.30 (t, $J$ = 5.2 Hz, 2H), 3.42−3.54 (m, 4H); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 17.4, 20.8,

(4) (a) Shechter, H.; Kirk, J. C. *J. Am. Chem. Soc.* **1951**, *73*, 3087−3091. (b) Smissman, E. E.; Bergen, J. V. *J. Org. Chem.* **1962**, *27*, 2316−2318. (c) Hirano, M.; Yakabe, S.; Satoh, A.; Clark, J. H.; Morimoto, T. *Synth. Commun.* **1996**, *26*, 4591−4596.
(5) Dave, V.; Warnhoff, E. W. *J. Org. Chem.* **1983**, *48*, 2590−2598.
(6) Badiang, J. G.; Aubé, J. *J. Org. Chem.* **1996**, *61*, 2484−2487.
(7) Corey, E. J.; Suggs, W. *Tetrahedron Lett.* **1975**, *31*, 2647−2650.
(8) Stork, G.; Brizzolara, A.; Landesman, H.; J., S.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207−222.
(9) Kharasch, M. S.; Sosnovsky, G. *J. Org. Chem.* **1958**, *23*, 1322−1326.

28.7, 28.8, 35.7, 42.9, 47.6, 57.6, 173.8; IR (neat) 3420, 2960, 1625 $cm^{-1}$; MS (FAB) *m/e* 172 ($M^+ + 1$), 154; HRMS calcd for $C_9H_{18}NO_2$ ($M^+ + 1$): 172.1331, found 172.1331.

***N*-Hydroxypropyl-6-methylvalerolactam (4b)**: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.27 (d, $J = 6.5$ Hz, 3H), 1.66−1.76 (m, 4H), 1.86−1.94 (m, 2H), 2.43 (m, 2H), 3.23 (dt, $J = 14.2$, 5.4 Hz, 1H), 3.41−3.57 (m, 4H), 3.86 (m, 1H); $^{13}C$ NMR (400 MHz, $CDCl_3$) $\delta$ 17.1, 19.8, 29.9, 30.5, 31.5, 40.7, 51.9, 58.2, 171.4; IR (neat) 3410, 2960, 1620 $cm^{-1}$; MS (FAB) *m/e* 172 ($M^+ + 1$), 154; HRMS calcd for $C_9H_{18}NO_2$ ($M^+ + 1$): 172.1338, found 172.1330.

**Reaction of 2-Methoxycyclopentanone with Azido Alcohol 1: *N*-Hydroxyethyl-3-methoxyvalerolactam (3m), *N*-Hydroxyethyl-6-methoxyvalerolactam (4m), and Bicyclic Side Product (6a)**. **Compound 3m**: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.73 (m, 1H), 1.88−1.98 (m, 3H), 3.27−3.50 (m, 7H), 3.65−3.74 (m, 4H); $^{13}C$ NMR (400 MHz, $CDCl_3$) $\delta$ 19.1, 26.9, 49.0, 50.5, 58.5, 60.7, 76.6, 170.5; IR (neat) 3410, 2960, 1640 $cm^{-1}$; MS (CI) *m/e* 174 ($M^+ + 1$), 143; HRMS calcd for $C_8H_{16}NO_3$ ($M^+ + 1$): 174.1130, found 174.1122. **Compound 4m**: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.66−1.78 (m, 2H), 1.98 (m, 1H), 2.10 (m, 1H), 2.32 (m, 1H), 2.49 (m, 1H), 3.36 (m, 4H), 3.76 (m, 4H), 4.51(t, $J = 2.7$ Hz, 1H); $^{13}C$ NMR (400 MHz, $CDCl_3$) $\delta$ 15.4, 25.6, 32.2, 50.9, 55.0, 61.5, 89.3, 171.6; IR (neat) 3400, 2960, 1635 $cm^{-1}$; MS (CI) *m/e* 174 ($M^+ + 1$), 142; HRMS calcd for $C_8H_{16}NO_3$ ($M^+ + 1$): 174.1130, found 174.1125. **Compound 6a**: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.47 (m, 1H), 1.68 (m, 1H), 1.92 (m, 2H), 2.29 (m, 2H), 2.46 (dd, $J = 11.9$, 6.1 Hz, 1H), 3.39 (m, 1H), 3.87 (m, 2H), 4.15 (m, 1H), 4.70 (dd, $J = 9.28$, 4.26 Hz, 1H); $^{13}C$ NMR (400 MHz, $CDCl_3$) $\delta$ 17.2, 28.1, 30.8, 42.5, 64.6, 87.4, 168.5; IR (neat) 3500, 2990, 1640 $cm^{-1}$; MS (CI) *m/e* 142 ($M^+ + 1$), 72; HRMS calcd for $C_7H_{12}NO_2$ ($M^+ + 1$): 142.0856, found 142.0868.

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**Supporting Information Available:** Additional experimental details, including characterization of new compounds, summary of regioisomer assignments, and X-ray data for compounds **8a** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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