# Amino Acid Derived Heterocycles: Lewis Acid Catalyzed and Radical Cyclizations from Peptide Acetals

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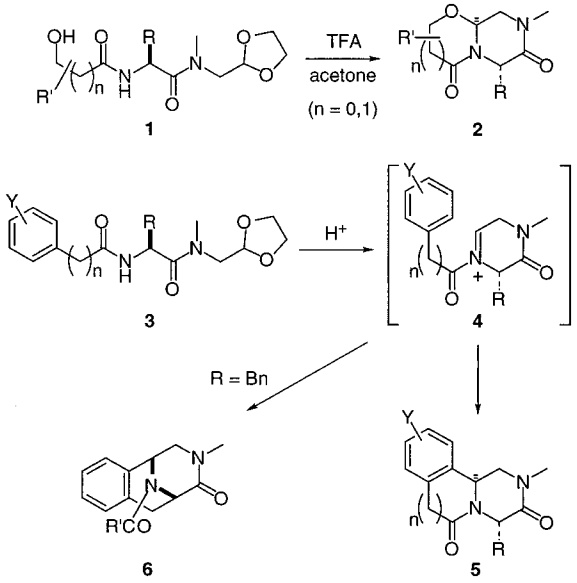
Bicyclization of peptide acetals via nucleophilic attack of a phenyl group on an endocyclic acyliminium ion **4** was explored as a route to novel amino acid derived heterocycles and peptidomimetic scaffolds. In the presence of protic acid, bridged structures such as **6** are formed readily from phenylalanine derivatives, but the fused-ring analogues **5** could not be obtained in good yield. In contrast, radical cyclization of the bromophenyl dihydropyrazinone **7** provides an effective alternative for the synthesis of **5** ($n$ = 0, 1, 2). Additional versatility in this process was demonstrated by efficient synthesis of a different fused ring system, represented by the antihelmintic praziquantel, **8**.

The cyclization of simple, peptide-based precursors to generate rigid scaffolds as peptidomimetics and combinatorial chemistry motifs has been the focus of several recent investigations.[1−3] In this context, we have described the efficient and stereoselective cyclization of acetal-containing *N*-(hydroxyacyl)amino acid analogues (e.g., **1**) in the presence of protic acid, leading to bicyclic lactams such as **2** (Scheme 1). Such readily varied structures show considerable promise as combinatorial motifs and as $\beta$-turn mimetics.[4]

We sought to extend this chemistry to encompass a new synthetic route (**3** → **5**) involving ring closure by nucleophilic attack of an aromatic ring on the acyliminium ion intermediate **4** instead of a heteroatom.[2,4−5] However, acid-catalyzed cyclization of the phenylalanine derivatives (e.g., **3**, R = Bn) does not generate the tricyclic ring system as anticipated; instead, the aromatic ring of the side chain attacks the cation to give the bridged structures **6**. The structure of this ring system was deduced by comparison with the *N*-acetyl derivative (**6**, R′ = Me) prepared in a similar fashion and assigned by X-ray analysis. This ring system is of potential interest as an alternative combinatorial template and bears some resemblance to the core of the saframycin antibiotic group.[6] A variety of conditions and substrates were thus explored to optimize the reaction and also to determine if closure to the fused-ring system could be favored.

**Scheme 1. Acid-Induced Cyclizations to Heterocycles 2, 5, and 6**




A range of common protic acids and solvent combinations was assayed for the cyclization, and methanesulfonic acid in nitromethane (1:4) was found to give the best results. The substrates were varied both in the length of the phenylacyl side chain and its electron density (Table 1), in the expectation that increasing either of these parameters would enable this aromatic ring to compete better with the amino acid side chain. Indeed, cyclization to the fused-ring isomer occurs to a limited extent when methoxy groups are attached to the phenylacetyl group (series **e** and **f**). However, three methoxy groups are required before this mode of cyclization predominates, and even then the reaction proceeds in low yield.

The preference for cyclization to the bridged- over the fused-ring system, which dominates electronic considerations, reflects conformational influences. A conformational search[7] of dihydropyrazinone **7d** (H in place of Br),

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**Table 1. Competition between Cyclization Pathways for Acyliminium Ions 4 (R = Bn)[a]**

| series | n | Y | yield of **5** (%) | yield of **6** (%) |
|---|---|---|---|---|
| **a** | 0 | 2-Br | 0 | 87 |
| **b** | 1 | H | 0 | 75 |
| **c** | 1 | 4-$NO_2$ | 0 | 72 |
| **d** | 1 | 2-Br | 0 | 79 |
| **e** | 1 | 3-MeO | 11[b] | 61 |
| **f** | 1 | 3,4,5-$(MeO)_3$ | 18[c] | 9[c] |
| **g** | 2 | H | 0 | 67 |

[a] Treatment of **4** (R = Bn) with $MeSO_3H/CH_3NO_2$ (1:4) at 60 °C for 16 h. [b] 1:1 mixture of regioisomers. [c] Isomers not separated.

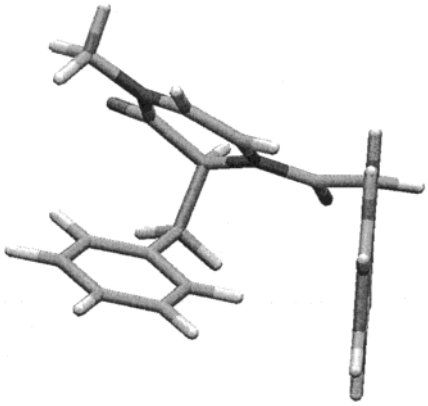

**Figure 1.** Minimum-energy conformation calculated for **7d** (des-Br).

as a mimic of the intermediate acyliminium species **4**, suggested that the phenylalanine side chain adopts the pseudoaxial position in order to minimize $A^{1,2}$ and $A^{1,3}$ strain from the flanking carbonyl groups (Figure 1), in analogy to the known conformational preferences of diketopiperazines.[8] As a consequence, this side chain is poised to attack the electrophilic center. Moreover, the rigidity of the exocyclic amide bond hinders effective p-orbital overlap for attack by the other aromatic ring.

The question remained as to whether the fused-ring cyclization of these simple phenylacetyl analogues (i.e., to give **5** rather than **6**) works with nonaromatic amino acid substrates. Accordingly, nonaromatic versions of **3** were synthesized (R = Me, $^i$Pr, i.e., utilizing the amino acids alanine and valine) and were subjected to the same acidic cyclization conditions as before. No compounds of type **5** were observed in the crude reaction mixture, and only enediamide was detected. When more vigorous heating was employed, decomposition of the enediamide occurred.

In light of the difficulty encountered in developing a general synthesis of the fused-ring system via the acyliminium intermediate, we turned to radical cyclization as an alternative approach (Scheme 2). The recent successes of Rigby[9a] and Ishibashi et al.[9] with the ring closure of aryl radicals onto acyclic enamides prompted

**Scheme 2. Lewis Acid and Radical-Based Approaches to Fused Ring Scaffold 5**

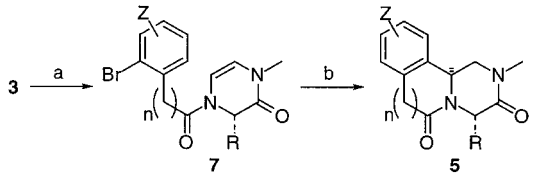


**Table 2. Formation of Dihydropyrazinones 7 and Radical Cyclization to Fused-Ring Products 5**

| series | n | Z | R | yield of **7**[a] (%) | yield of **5**[b] (%) |
|---|---|---|---|---|---|
| **a** | 0 | H | Bn | 14 | 64 |
| **d** | 1 | H | Bn | 88 | 80 |
| **h** | 1 | H | *i*-Pr | 87 | 70 |
| **i** | 1 | H | Me | 88 | 71 |
| **j** | 2 | 4,5-$(MeO)_2$ | Bn | 82 | 28 |

[a] 10 mol % $Sn(OTf)_2$, acetone, 40 °C, 32 h. [b] $Bu_3SnH$, AIBN, toluene, 110 °C, 16 h.

us to apply this strategy to the acyl pyrazinone intermediate **7**. These cyclic enediamides are readily formed from the linear peptide acetals **3** on treatment with catalytic tin(II) trifluoromethanesulfonate (Table 2). The conditions are mild, the yields are usually over 80%, and purification can be accomplished by filtration through a plug of silica gel. The brominated analogue **7b** is cyclized in high yield with $Bu_3SnH$/AIBN in refluxing toluene to generate the fused-ring product **5b** as a single diastereomer. This structure was confirmed by single-crystal X-ray diffraction. The pseudoaxial amino acid side chain directs the reaction by blocking one face of the pyrazinone double bond, leading to the observed cis relationship between amino acid side chain and bridgehead hydrogen. High stereoselectivity was also observed with the valine- and alanine-derived substrates (**7h** and **7i**), so the same relative configuration is inferred for the products.

Cyclization of the corresponding 3-(2-bromophenyl)-propanoyl (**7j**) and 2-bromobenzoyl (**7a**) derivatives afford the ring-expanded and -contracted systems **5j** and **5a**, respectively. The latter ring system is less planar than **5d**, from X-ray analysis, and the central piperazinone ring displays interesting geometrical properties. The cis relationship and proximity of the phenylalanine side chain to the bridgehead hydrogen in **5a** result in an upfield chemical shift of 1.5 ppm for this hydrogen in the $^1$H NMR spectrum, in comparison to **5b**. The major side reaction in formation of the seven-membered analogue **5j** is simple debromination, reflecting competition from intermolecular reduction of the radical when intramolecular addition to the double bond is less facile.

The ring system of **5** bears some relationship to that of the antihelmintic drug praziquantel, **8** (Scheme 3), a simple but effective antihelmintic used worldwide in the treatment of schistosomiasis (bilharzia).[10] The ring systems differ in the positions of the carbonyl groups, although in principle they should be accessible by similar chemistry. Indeed, the syntheses that have been reported to date rely on a final Friedel−Crafts ring closure

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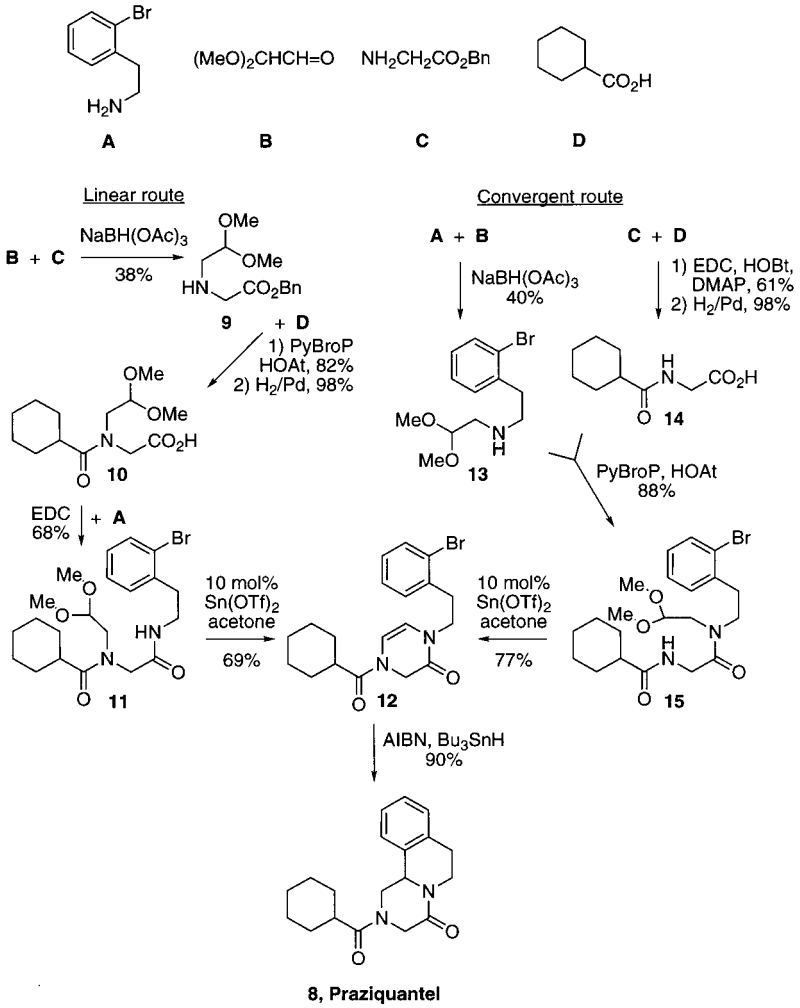
**Scheme 3. Synthesis of Praziquantel 8 by Radical Cyclization**




mediated by strong acid.[11] To explore the versatility of the pyrazinone radical cyclization reaction, we applied it to a synthesis of praziquantel (Scheme 3). The milder conditions of this route have the attraction that ready incorporation of amino acids other than glycine can be envisaged as a point of diversity.[12]

Two routes to the pyrazinone intermediate **12** were investigated, by analogy to those reported by Kim et al. for the des-bromo analogues.[11a] These routes differ in their degree of convergence and in the direction of acetal cyclization (Scheme 3). The acetal unit was introduced by reductive amination with dimethoxyacetaldehyde, either in combination with benzyl glycinate (linear route) or *o*-bromophenethylamine (convergent route). Although this reaction proceeded in modest yield, it comes early in the synthesis and was not optimized. The secondary amines **9** and **13**, respectively, were subjected to the appropriate amide coupling reactions to afford the isomeric acetal cyclization precursors **11** and **15**. Both underwent tin triflate-catalyzed ring closure to the pyrazinone **12** in good yield, although the cyclization of **15** proceeded more cleanly than that of its isomer **11**. These cyclizations are analogous to the methanesulfonic acid-catalyzed reactions reported previously for the des-bromo series,[11a] although the tin triflate procedure described here is milder and potentially more applicable to functionalized analogues. The radical-initiated cyclization of pyrazinone **12** proceeded smoothly in 90% yield to give **8**, with spectral characteristics identical to those reported for praziquantel.[13] We envisage that the peptide acetal chemistry described here could be applied to the construction of praziquantel analogues that possess more diverse functionality.

The peptide aldehyde-derived acyliminium and pyrazinone intermediates thus provide facile entry into a range of novel heterocyclic structures. The chemistry is robust and simple, and generates stable, rigid scaffolds with a range of potential applications in peptidomimetic and combinatorial chemistry. Moreover, the results we describe suggest that other stereoselective addition reactions involving the pyrazinone double bond can be developed for similar purposes.

## Experimental Section

Experimental procedures for representative steps are described below; full details, including characterization, for other compounds are provided in the Supporting Information. Coordinates for structures **5a**, **5d**, and **6** have been deposited with the Cambridge Crystallographic Data Centre (http://www.ccdc.cam.ac.uk/).

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**1-Benzyl-3-methyl-4,4a-dihydro-3*H*-3,9a-diazafluorene-2,9-dione (5a).** A deoxygenated solution of the enediamide **7a** (41 mg, 0.11 mmol), AIBN (4.5 mg, 0.25 equiv), and tributyltin hydride (43 $\mu$L, 1.5 equiv) in degassed toluene (6 mL) was heated at reflux for 16 h. The reaction mixture was allowed to cool to room temperature and concentrated in vacuo, and the residue was purified by flash column chromatography (7:3 EtOAc/pet ether → EtOAc) to give the dione **5a** as white needles (21 mg, 64%): mp 128−131 °C; $R_f$ (EtOAc) 0.23; IR (mull) 1699, 1650, 1615, 1495 cm$^{-1}$; $^1$H NMR $\delta$ 7.90 (m, 1), 7.53 (m, 2), 7.28 (m, 1), 7.18 (m, 3), 7.12 (m, 2), 5.08 (t, 1, $J$ = 5.0 Hz), 3.79 (dd, 1, $J$ = 11.0, 4.5 Hz), 3.66 (dd, 1, $J$ = 13.5, 4.0 Hz), 3.49 (dd, 1, $J$ = 12.0, 4.5 Hz), 3.29 (dd, 1, $J$ = 13.5, 5.5 Hz), 3.05 (apparent t, 1, $J$ = 11.5 Hz), 3.03 (s, 3); $^{13}$C NMR $\delta$ 166.8, 166.3, 141.7, 136.8, 132.3, 131.7, 129.8, 129.1, 128.5, 126.8, 124.2, 122.0, 55.1, 53.5, 52.7, 37.7, 35.7; HRMS (FAB) calcd for $C_{19}H_{18}N_2O_2$ ($MH^+$) 307.1447, found 307.1453.

**13-(2-Bromobenzoyl)-11-methyl-11,13-diazatricyclo-[7.3.1.0$^{2,7}$]trideca-2(7),3,5-trien-10-one (6a).** A solution of phenylalanine derivative **3a** ($n$ = 0, R = Bn, Y = 2-Br) (100 mg, 0.22 mmol) in 4:1 nitromethane/methanesulfonic acid (10 mL) was heated at 60 °C for 20 h and then allowed to cool to room temperature. The mixture was partitioned between 5% aqueous $NaHCO_3$ and $Et_2O$, and the aqueous phase was extracted with $Et_2O$ (3 × 20 mL). The combined organic portions were washed with brine (20 mL), dried ($MgSO_4$), and evaporated, and the resultant oil was purified by flash column chromatography (EtOAc → 9:1 EtOAc/acetone) to give the bridged dione **6a** as a clear, colorless oil (75 mg, 87%): $R_f$ (EtOAc) 0.28; $^1$H NMR (two amide rotamers) $\delta$ 6.9−7.6 (m, 8), 6.00 (d, $J$ = 4.5 Hz) and 4.60 (dd, $J$ = 14.5, 4.0 Hz) (1 total), 4.25 (br d, $J$ = 5.0 Hz) and 5.57 (t, $J$ = 6.0 Hz) (1 total), 4.30 (t, $J$ = 4.5 Hz) and 4.14 (dd, 1, $J$ = 11.5, 4.5 Hz) (1 total), 3.29 (d, $J$ = 12 Hz) and 3.23 (d, $J$ = 12 Hz) (1 total), 3.07 (m, 2), 2.85 (s, 3); $^{13}$C NMR $\delta$ 167.6, 167.3, 166.1, 136.2, 133.8, 133.0, 132.3, 131.0, 130.9, 129.1, 128.1, 128.0, 127.4, 127.2, 126.8, 119.3, 71.4, 66.5, 60.6, 55.7, 55.4, 53.0, 52.7, 50.9, 47.2, 37.8, 37.5, 34.3, 33.2; MS (FAB) $m/z$ 385, 387 (14, $MH^+$), 183, 185 (100); HRMS (FAB) calcd for $C_{19}H_{18}BrN_2O_2$ ($MH^+$) 385.0545, found 385.0552.

**3-Benzyl-4-[2-(2-bromophenyl)acetyl]-1-methyl-3,4-dihydro-1*H*-pyrazin-2-one (7d).** A solution of phenylalanine derivative **3d** ($n$ = 1, R = Bn, Y = 2-Br) (100 mg, 0.22 mmol) and tin(II) trifluoromethanesulfonate (9 mg, 10 mol %) in acetone (8 mL) was heated at 40 °C for 40 h. After being cooled to room temperature, the reaction mixture was concentrated in vacuo, the residue was dissolved in EtOAc, and the solution was passed through a short plug of silica (eluting with EtOAc) and concentrated in vacuo to yield the enediamide **7d** as a white powder (69 mg, 80%): $R_f$ (EtOAc) 0.58; $^1$H NMR (mixture of rotamers) $\delta$ 7.54 (d, $J$ = 8.0 Hz) and 7.46 (d, $J$ = 8.0 Hz) (1 total), 7.36 (m, 1), 7.21 (m, 4), 7.12 (m, 2), 7.05 (m, 1), 6.70 (d, $J$ = 6.0) and 5.97 (dd, $J$ = 5.5, 1.5 Hz) (1 total), 5.79 (d, $J$ = 6.0 Hz) and 5.49 (t, $J$ = 7.0 Hz) (1 total), 5.37 (d, $J$ = 6.0 Hz) and 4.78 (t, $J$ = 8.0 Hz) (1 total), 3.75 + 3.8 (ABq, $J$ = 16.0 Hz) and 3.44 + 3.04 (ABq, $J$ = 16.5 Hz) (2 total), 3.16 (s), 3.07 (s) (total 3), 3.04 (m, 2); $^{13}$C NMR $\delta$ 168.5, 167.6, 165.4, 164.6, 135.9, 133.8, 132.7, 132.5, 131.3, 130.9, 129.9, 129.6, 129.1, 128.8, 128.7, 128.1, 127.7, 127.6, 127.3, 126.8, 124.6, 116.4, 115.4, 107.9, 107.8, 60.9, 56.3, 40.4, 39.2, 36.3, 35.8, 33.6, 33.4; MS (FAB) $m/z$ 401.0 (39, doublet, $MH^+$); HRMS (FAB) calcd for $C_{20}H_{20}BrN_2O_2$ ($MH^+$) 399.0708, found 399.0712.

**2-(Cyclohexanecarbonyl)-5,6,10b,4a-tetrahydropiperazino[2,1-*a*]isoquinolin-4-one (8, Praziquantel).** A solution of enediamide **12** (100 mg, 0.26 mmol), AIBN (11 mg, 0.25 equiv), and tributyltin hydride (103 $\mu$L, 1.5 equiv) in degassed toluene (25 mL) was heated at reflux for 16 h, allowed to cool to room temperature, and concentrated in vacuo. The residue was purified by flash column chromatography (1:1 EtOAc/pet ether → EtOAc) to give praziquantel as white plates (72 mg, 90%); approximate 1:3 ratio of rotamers: mp 132−5 °C (lit.[14] 132−3 °C); $^1$H NMR $\delta$ 7.22 (m, 4), 5.14 (dd, 1, $J$ = 13.5, 2.5 Hz), 4.79 (m, 2), 4.45 (d, $J$ = 17.5 Hz), 4.35 (d, $J$ = 12.5 Hz) (total 1), 4.06 (d, $J$ = 17.5 Hz), 3.83 (d, $J$ = 18.5 Hz) (total 1), 3.23 (t, $J$ = 12.0 Hz), 2.85 (m) (total 4), 2.55 (m), 2.44 (m) (total 1), 1.76 (m, 5), 1.52 (m, 2), 1.26 (m, 3); $^{13}$C NMR $\delta$ 174.7, 164.3, 134.7, 132.7, 129.2, 127.4, 126.9, 125.4, 54.9, 49.0, 45.1, 40.7, 39.0, 29.2, 28.9, 28.7, 25.7; MS (FAB) $m/z$ 313 ($MH^+$, 100), 203 (28); HRMS (FAB) calcd for $C_{19}H_{25}N_2O_2$ ($MH^+$) 313.1916, found 313.1916.

**1-[2-(2-Bromophenyl)ethyl]-4-(cyclohexanecarbonyl)-1,3,4-trihydropyrazin-2-one (12) from Cyclization of 15.** A solution of peptide acetal **15** (332 mg, 0.73 mmol) and tin(II) triflate (29 mg, 0.1 equiv) in acetone (25 mL) was stirred at 40 °C for 2 d and then concentrated in vacuo. The residue was taken up in EtOAc (2 mL) and passed through a plug of silica, eluting with EtOAc. The eluent was concentrated in vacuo to give the enediamide as a white powder (218 mg, 76%); approximate 1:5 ratio of rotamers: $^1$H NMR $\delta$ 7.50 (d, 1, $J$ = 8.0 Hz), 7.19 (m, 2), 7.08 (m, 1), 6.59 (d, $J$ = 6.5 Hz), 6.08 (d, $J$ = 6.5 Hz) (total 1), 5.49 (d, $J$ = 6.5 Hz), 5.38 (d, $J$ = 6.0 Hz) (total 1), 4.29 (s, 2), 3.73 (t, 2, $J$ = 7.5 Hz), 3.02 (t, 2, $J$ = 7.0 Hz), 2.43 (tt, 1, $J$ = 12.0, 3.5 Hz), 1.74 (m, 5), 1.46 (m, 2), 1.22 (m, 3); $^{13}$C NMR $\delta$ 173.7, 163.6, 137.4, 132.9, 131.3, 128.5, 127.7, 124.5, 113.8, 108.9, 45.9, 45.8, 40.8, 34.6, 28.8, 25.6, 25.6; MS (ESMS) $m/z$ 413 (30, d, $MNa^+$), 391 (100, d, $MH^+$); HRMS (FAB) calcd for $C_{19}H_{24}BrN_2O_2$ ($MH^+$) 391.1021, found 391.0986.

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**Supporting Information Available:** Experimental conditions and characterization of precursors and other analogues. This material is available free of charge via the Internet at http://pubs.acs.org.

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