Synthesis of Porphobilinogen via a Novel Ozonide Cleavage Reaction

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Abstract: Porphobilinogen lactam methyl ester (**3a**) has been prepared in seven steps, and ∼20−30% overall yield, beginning with furfurylamine (**4a**).[24] Hydrolysis of **3a** following the literature procedure then gave porphobilinogen (**1**). A key intermediate in our synthesis of **3a** is the 7-oxonorbornene derivative **7a**, which was derived from **4a** utilizing a tandem Johnson ortho ester Claisen rearrangement followed by intramolecular Diels−Alder cyclization (five steps, 55−65%).[24] Interesting steric accelerating effects were observed in this sequence. Conversion of **7a** to **3a** was then accomplished employing a novel ozonide cleavage/oxidation reaction, which generated tetrahydrofurans **16a**, **32**, and **33** in the proper oxidation state for direct aminolysis to pyrrole **3a**. A mechanism is proposed for the ozonide cleavage/oxidation that accounts for the observed stereoselectivity of this step.

Introduction

Porphobilinogen (**1**) is a naturally occurring heterocycle that is the biosynthetic precursor to nearly all biologically important tetrapyrroles (Figure 1). Although **1** was initially isolated and

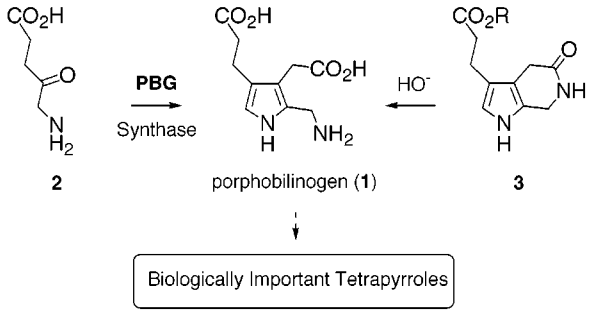


Figure 1. Biosynthesis and synthesis of pohobilinogen) (**1**).

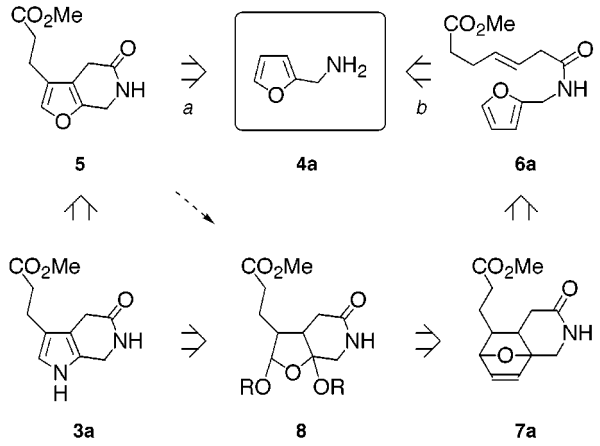
characterized nearly fifty years ago,[1a] it continues to attract considerable attention.[1] Partly this is because of its utility as a building block for complex bilanes,[2] and also due to its potential medical value (photodynamic therapy;[3] treatment of acute Pb poisoning[4]). In nature **1** is derived by enzyme-mediated dimerization of aminolevulinic acid (**2**), a transformation that is difficult to mimic in vitro.[1l] The most efficient laboratory precursor to **1** is porphobilinogen lactam ester **3** (R = Me, Et), which affords **1** upon base hydrolysis.[1d,g,h,k,5] However, a practical synthesis of this deceptively simple compound remains elusive, and costs for **1** can range over $10 000 per gram.[6]

Results and Discussion

Several issues need to be addressed in the synthesis of **1**. These include regiochemical control about the pyrrole ring, and the practical considerations of dealing with insoluble and often highly unstable intermediates.[1c] Also, most of the published routes to **1** employ toxic and/or expensive reagents, such as cyanide and isocyanides.[1] In this paper we describe a synthesis of **1** using simple starting materials, suitably derivatized for ease of isolation and purification.

Our synthesis of **1** began with furfurylamine (**4a**) (Scheme 1), which is available in bulk quantities by reductive amination of 2-furaldehyde (derived from cereal straws and corncobs).[7]

Scheme 1



We evaluated two strategies for converting **4a** to porphobilinogen lactam ester **3a**, a known precursor to **1**.[1c,h,5] One of these involved elaboration of **4a** to the furanolactam **5** (path a), which is in the proper oxidation state for direct aminolysis to **3a**.[8] More likely, however, pyrrole formation would require initial conversion of **5** to the tetrahydrofuran **8**, via oxidative addition of ROH followed by catalytic hydrogenation.[8b] Acetals of type **8** should be more efficient precursors to **3a**, since they lack the aromatic stabilization present in furan **5**.[8a] We also envisioned a more direct route to **8** via oxidative cleavage of the 7-oxonorbornene

(1) (a) Isolation: Westall, R. G. *Nature* **1952**, *170*, 614. Syntheses: (b) Neier, R. *J. Heterocycl. Chem.* **2000**, *37*, 487 and references therein. (c) de Leon, C. Y.; Ganem, B. *Tetrahedron* **1997**, *53*, 7731. (d) Adamczyk, M.; Rajarathnam, R. E. *Tetrahedron Lett.* **1995**, *36*, 9121. (e) Faber, K.; Anderson, H. J.; Loader, C. E.; Daley, A. S. *Can. J. Chem.* **1984**, *62*, 1046. (f) Scott, A. I. *Pure Appl. Chem.* **1981**, *53*, 1215. (g) Jones, M.; Froussions, C.; Evans, D. A. *J. Chem. Soc. Chem. Commun.* **1976**, 472. (h) Kenner, G. W.; Smith, K. M.; Unsworth, J. F. *J. Chem. Soc. Chem. Commun.* **1973**, 43. (i) Battersby, A. R.; Hunt, E.; McDonald, E.; Moron, J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2917. (j) Frydman, B.; Reil, S.; Despuy, M. E.; Rapoport, H. *J. Am. Chem. Soc.* **1969**, *91*, 2338. (k) Jackson, A. H.; MacDonald, S. F. *Can. J. Chem.* **1957**, *35*, 715. (l) Muller, G. *Z. Naturforsch. B.* **1972**, *27*, 473.

(2) Xue, T.; Scott, A. I. *Tetrahedron Lett.* **1998**, *39*, 6651.

(3) Grant, W. E.; Hopper, C.; MacRobert, A. J.; Speight, P. M.; Brown, S. G. *Lancet* **1993**, *342*, 147.

(4) Gibbs, P. N. B.; Chaudhry, A. G.; Jordan, P. M. *Biochem. J.* **1985**, *230*, 25. See also ref 1c.

(5) Battersby, A. R.; Fookes, C. J. R.; Meegan, M. J.; McDonald, E.; Wurziger, H. K. W. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2786.

(6) See, for example: (a) Aldrich Chemical Catalog, 1999; (b) Fluka Chemical Catalog, 1997.

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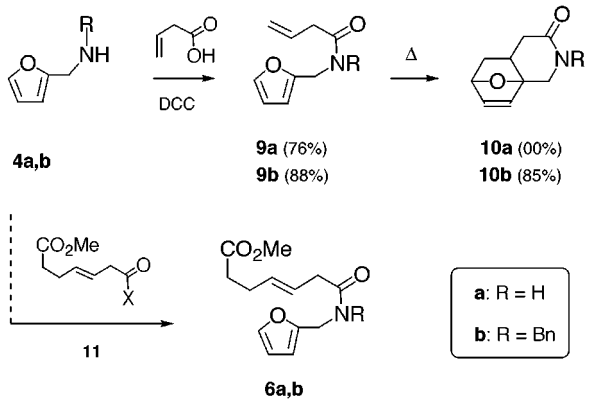
derivative **7a** (path b). In principle, **7a** could be derived by intramolecular Diels−Alder cyclization (IMDA) of the alkene amide **6a**, although substrates of this type are often relatively unreactive.[9]

The viability of path b was first tested with the simple furan derivative **9a** (Scheme 2), obtained by DCC-induced coupling of **4a** with 3-butenoic acid (76%). Our initial experiments were

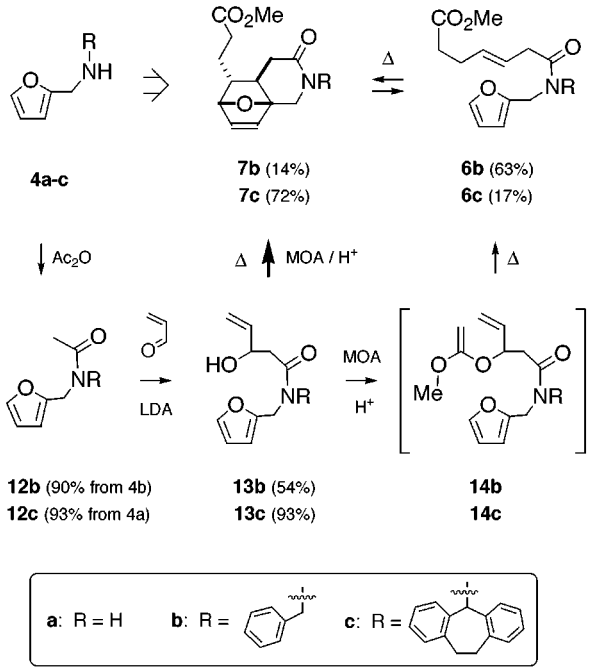
Scheme 2



not promising. Furan **9a** was very sluggish toward cyclization, affording only trace amounts of the desired adduct **10a** at temperatures up to 180 °C (at this point double bond migration interceded). Fortunately, however, the *N*-benzyl derivative **9b** was much more reactive, and gave an 85% yield of **10b** after 72 h at 120 °C. Many examples of such sterically[10] (and/or conformationally[11]) accelerated IMDA reactions have been reported. Evidence for a "facilitated transition state" has also been described.[11c] Thus encouraged, we set out to prepare the porphobilinogen precursor **6b** (R = Bn), a seemingly trivial step involving acylation of *N*-benzylfurfurylamine (**4b**) with an appropriate dicarboxylic acid derivative **11** (Scheme 2; X = OH, Cl, etc.). However, the synthesis of **11** turned out to be unexpectedly difficult.

Much better results were obtained following the pathway outlined in Scheme 3. Thus, *N*-benzylfurfurylamine (**4b**) was

Scheme 3



converted to the allylic alcohol **13b** in straightforward fashion by acylation (Ac_2O/pyridine; 90%), followed by condensation of **12b** with acrolein (54%). Alcohol **13b** was then transformed directly to the target furanamide **6b** by Johnson ortho ester Claisen rearrangement, employing methylorthoacetate (MOA) in hot toluene/H^+ (77%).[12] The presumed intermediate in this reaction, ketene acetal **14b**, was not isolated. Interestingly, upon prolonged heating (120−30 °C) of **13b** with MOA we obtained mixtures of **6b** (63%) and the target 7-oxonorbornene **7b** (14%), which appeared to represent an equilibrium ratio (i.e. little change from 24 to 90 h). Since we were unable to improve upon the ratio of **7b**:**6b** produced in this manner, we explored the effect of different substituents "R" on the Diels−Alder cyclization. From among many trials (R = TBDMS, trityl, 2,4,6-trimethylbenzyl, acetyl, fluorenyl, and others), we were pleased to find that the case of R = dibenzosuberyl provided the desired combination of stability, ease of isolation, and reactivity.[13] The requisite allylic alcohol **13c** was prepared in three steps from furfurylamine (**4a**), by alkylation with suberyl chloride and in situ acylation (93%), followed by condensation with acrolein (93%). Heating **13c** for 72 h (130 °C) with MOA/toluene/pivalic acid then gave a 72% yield of **7c** (84% based on recovered **6c**), along with 17% of **6c** that could be recycled. Control experiments showed that the ratio of **7c**:**6c** was thermodynamically governed, since essentially the same mixture was obtained upon heating adduct **7c**.[14] This four-step conversion of furfurylamine (**4a**) to 7-oxonorbornene **7c** can be conveniently carried out on multigram scales, and affords **7c** in >60% overall yield.

We next addressed the issue of timing in removal of the activating *N*-dibenzosuberyl group. In the case of **7c** deprotection was accomplished in 85−95% yield upon brief treatment with TFA/anisole (Figure 2).[13a,24] Lactam **7a** was obtained as a

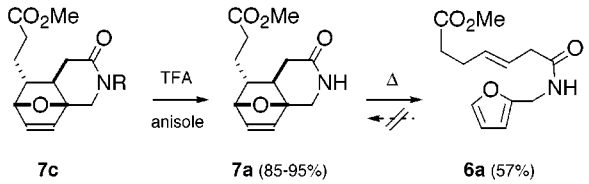


Figure 2. Cleavage of **7c** (R = SUB). Cycloreversion of **7a**.

crystalline solid (in principle, the suberyl group can be

(7) (a) Adams, R.; Voorhees, V. *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. I, 274. (b) Robinson, J. C.; Snyder, H. R. *Org. Synth.* **1943,** *23*, 68.

(8) (a) Bak, B.; Pedersen, T.; Soerensen, G. O. *Acta Chem. Scand.* **1964**, *18*, 275. (b) Elming, N.; Clauson-Kaas, N. *Acta Chem. Scand.* **1952**, *6*, 867.

(9) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179.

(10) Choony, N.; Dadabhoy, A.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2017.

(11) (a) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224 and references therein. (b) McNelis, B. J.; Sternbach, D. D.; MacPhail, A. T. *Tetrahedron* **1994**, *50*, 6767. (c) Parrill, A. L.; Dolata, D. P. *Tetrahedron Lett.* **1994**, *35*, 7319. See also ref 9.

(12) (a) Johnson, W. S.; Wethemann, L.; Bartlett, W. R.; Brocksom, T. J.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741. (b) Heathcock, C. H.; Finkelstein, B. L.; Jarvi, E. T.; Radel, P. A.; Hadley, C. R. *J. Org. Chem.* **1988**, *53*, 1922.

(13) (a) Pless, J. *Helv. Chim. Acta* **1976**, *59*, 499. (b) van der Stelt, C. *Chem. Abstr.* **1963**, *61*, 3445b.

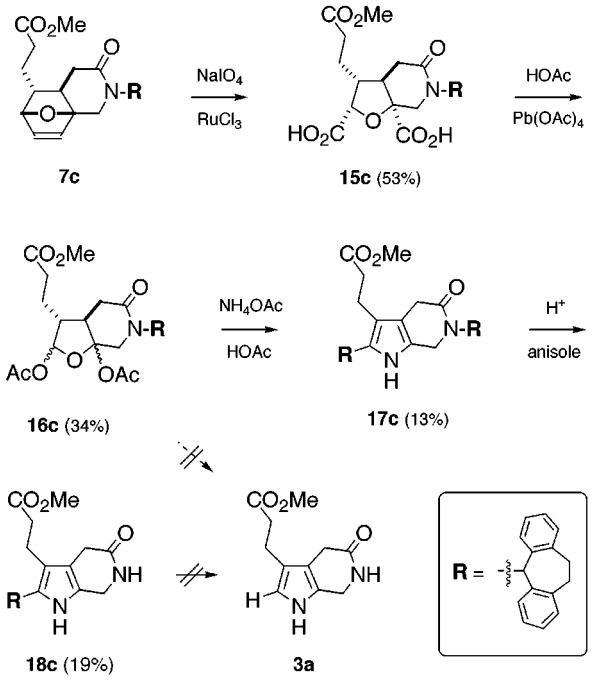
(14) All equilibration studies were performed at 130 °C.

(15) (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. See also: (b) Oguchi, T.; Ura, T.; Ishii, Y.; Ogawa, M. *Chem. Lett.* **1989**, 857. (c) Sam, D. J.; Simmons, H. E. *J. Am. Chem. Soc.* **1972**, *94*, 4024. (d) Wolfe, S.; Hasan, S. K.; Campell, J. R. *J. Chem. Soc. Chem. Commun.* **1970**, 1420. (e) Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4745. (f) Suga, T.; Rudloff, E. V. *Can. J. Chem.* **1969**, *47*, 3682. (g) Ben, R. N.; Breau, L.; Bensimon, C.; Durst, T. *Tetrahedron* **1994**, *50*, 6061.

recycled).[13b] Interestingly, however, prolonged thermolysis (130 °C) of **7a** led to nearly complete cycloreversion and gave the alkene amide **6a** (57%), along with decomposition products. In contrast to the substituted amides **6b** and **6c** (cf. Scheme 3), **6a** was inert toward cyclization. This result further corroborates the activating influence of bulky substituents "R" in Diels–Alder substrates of type **6**.

We also explored the possibility of maintaining the *N*-dibenzosuberyl group as long as practical, since it imparted good solubility properties to **7c** and subsequent intermediates. However, we were concerned that deprotection at a later stage might be complicated by the reactivity of the pyrrole ring in **3a**. This proved to be the case in our initial experiments (Scheme 4).

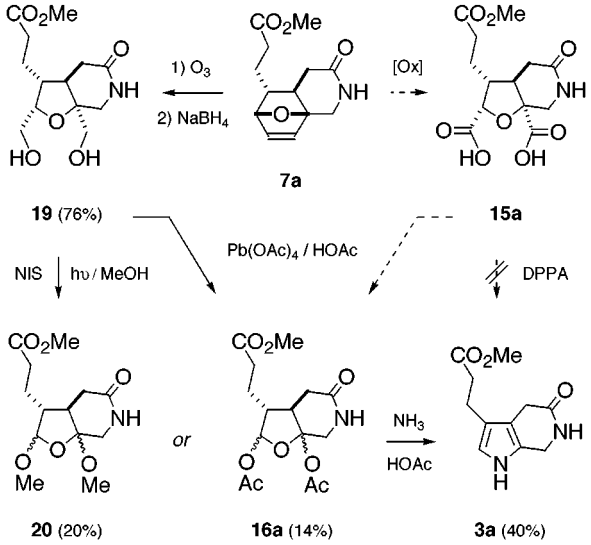
Scheme 4



Thus, oxidative cleavage of **7c** gave a 53% yield of the dicarboxylic acid **15c** ($NaIO_4$,/$RuCl_3$),[15a] which was further transformed to the diacetoxy compound **16c** upon treatment with $Pb(OAc)_4$ (34%).[16] Neither of these steps was optimized. Due to the acid-lability of the *N*-dibenzosuberyl group we were unable to effect the final conversion of **16c** to **3a**. All experiments involving amination of **16c** gave mixtures of **17c** and **18c**, where a dibenzosuberyl group had migrated to the incipient α-free position of the pyrrole ring.[17] Although it was possible to cleave the *N*-dibenzosuberyl group in **17c** to afford **18c** (TFA/anisole; 19%),[13a] attempted protonolysis of **18c** to **3a** caused extensive decomposition.

In view of the acid-lability of **16c** and congeners, we examined a similar set of cleavage reactions with the unsubstituted 7-oxonorbornene **7a** (Scheme 5). As expected, solubility properties were more of an issue in this series. For example, while oxidation of **7a** with $NaIO_4$/$RuCl_3$ appeared to produce the diacid **15a** (NMR, TLC),[15a] it was extremely difficult to isolate this material in pure form. Similar results were obtained with a variety of reagents known to cleave alkenes to carboxylic acids.[15] In addition, all experiments employing crude **15a** were inconclusive. Among others, these included oxidative decarboxylation to produce the diacetoxy derivative **16a** [$Pb(OAc)_4$],[16] and several attempts at inducing a bis-Curtius rearrangement with diphenylphosphoryl azide (DPPA).[18] This last transformation was attractive since it might produce the pyrrole **3a** directly upon acid workup (**15a** → **3a**). Somewhat better results were obtained with the bis-alcohol **19**, which was conveniently derived from **7a** by ozonolysis and in situ reduction ($NaBH_4$, 76%).[19] This material was nicely crystalline, and gave modest yields of the alkoxy-radical fragmentation products **20** (NIS, hυ, MeOH; 20%) and **16a** [$Pb(OAc)_4$, HOAc; 14%] using literature conditions.[20] Although far from efficient, we were able to demonstrate the viability of our strategy by converting both **20** and **16a** to porphobilinogen lactam methyl ester (**3a**) by aminolysis in HOAc/H_2O (40%).[21]

Scheme 5



We eventually developed a more direct means for converting **7a** to **16a**, based upon the ozonide photolysis studies of Story et al. (Figure 3).[22] These workers showed that photochemical

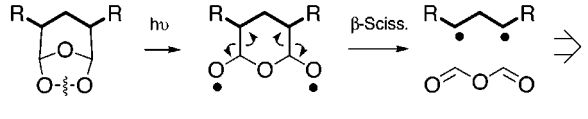


Figure 3. Photochemical cleavage of Ozonides **21**.[22a,b]

(or thermal) cleavage of ozonides **21** produces carbon-centered diradicals of type **23**, which are valuable intermediates for the

(16) Moore, J. A.; Partain, E. M., III *Org. Prep. Proced. Int.* **1980**, *12*, 305.

(17) For a similar example see ref 1 g. Attempted deprotection of **6c** (Scheme 3) also caused migration of the dibenzosuberyl group to the furano 5-position.

(18) (a) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151. (b) Jacobi, P. A.; Murphree, S.; Rupprecht, F.; Zheng, W. *J. Org. Chem.* **1996**, *61*, 2413.

(19) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 1396.

(20) (a) McDonald, C. E.; Holcomb, H.; Leathers, T.; Ampadu-Nyarko, F.; Frommer, J. *Tetrahedron Lett.* **1990**, *31*, 6283. (b) Gethin, D. M.; Simpkins, N. S. *Tetrahedron* **1997**, *53*, 14417.

(21) Alello, E.; Dattolo, G.; Cirrincione, G.; Plescia, S.; Daidone, G. *J. Heterocycl. Chem.* **1979**, *16*, 209.

(22) (a) Story, P. R.; Morrison, W. H.; Hall, T. K.; Farine, J.; Bishop, C. E. *Tetrahedron Lett.* **1968,** *9*, 3291. (b) Story, P. R.; Hall, T. K.; Morrison, W. H.; Farine, J. *Tetrahedron Lett.* **1968**, *9*, 5397. See also: (c) Hull, L. A.; Hisatsune, I. C.; Heicklen, J. *J. Phy. Chem.* **1972**, *76*, 2659.

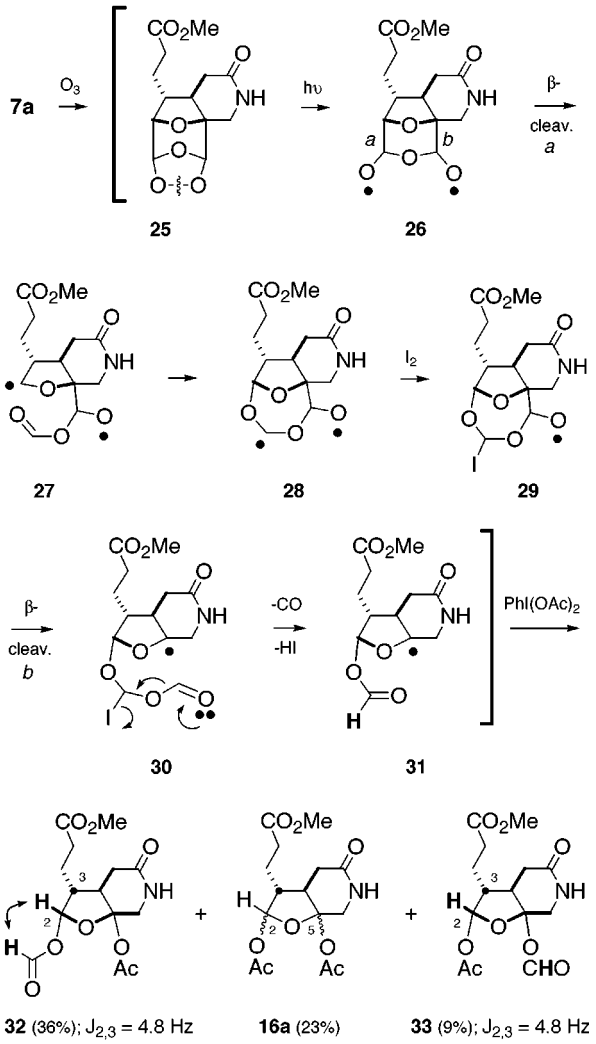
(23) (a) Armas, P.; Francisco, C. G.; Suarez, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 772. (b) Rigby, J. H.; Payen, A.; Warshakoon, N. *Tetrahedron Lett.* **2001**, *42*, 2047. (c) Francisco, C. G.; Freire, R.; Gonzalez, C. C.; Suarez, E. *Tetrahedron: Asymmetry* **1997**, *8*, 1971. (d) Mihailovic, M. L.; Lorenc, L.; Gasic, M.; Rogic, M.; Melera, A.; Stefanovic, M. *Tetrahedron* **1996**, *7*, 2345.

(24) Yields represent a range from several runs.

synthesis of cyclopropanes.[22] The initial step in this process is homolytic cleavage of the labile peroxide bond (**21** → **22**), followed by "double β-scission" to afford diradicals **23** and formic anhydride (**24**).[22a,b] This process was also investigated by Hull et al., with similar results.[22c] To the best of our knowledge, however, the oxidative trapping of such diradicals has not been reported. In principle this would provide a very short route from 7-oxonorbornene **7a** to acetals of type **16a**.

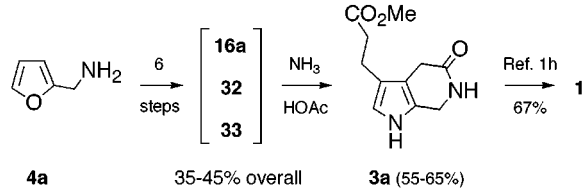
The successful realization of this strategy is outlined in Scheme 6. We tested many combinations of both thermal and photochemical cleavage of ozonide **25**, together with various oxidants [$PhI(OAc)_2$,[23a] $Pb(OAc)_4/Cu(OAc)_2$,[23b] PhIO,[23c] $Pb(OAc)_4/I_2$,[23d] $PhI(OTFA)_2/I_2$, and others].[23] Among these, photolysis and oxidation using *both* I_2 and iodosylbenzene diacetate [$PhI(OAc)_2$] provided the best results.[23a] In practice, 7-oxonorbornene **7a** was initially converted to the ozonide **25** at −78 °C (CH_2Cl_2; residual O_3 removed by purging with O_2). The reaction was then warmed slowly to room temperature, treated with excess $I_2/PhI(OAc)_2$, and photolyzed by using a 200 W tungsten lamp (vigorous stirring). Under these conditions we consistently obtained 65−75% yields of the acetals **16a**, **32**, and **33**, with the mixed acetal **32** predominating.[24] Initially these products were isolated and characterized. However, in practice it was more expedient to subject the mixture directly to aminolysis.

Scheme 6



Formates **32** and **33** were particularly reactive toward amination, which enabled us to improve upon our earlier results in Scheme 5. Thus, aminolysis of a mixture of **16a**, **32**, and **33** with $NH_4OAc/HOAc/H_2O$ (55 °C) afforded 50−65% of porphobilinogen lactam methyl ester (**3a**) (Scheme 7).[24] Since acetals **16a**, **32**, and **33** were prepared in six steps (35−45% overall) from furfurylamine (**4a**), the present synthesis of **3a** requires seven steps, and gives **3a** in ∼20−30% overall yield from **4a**.[24] Lactam **3a** has previously been converted to porphobilinogen (**1**) in 67% yield.[1h]

Scheme 7



Finally, the stereoselective formation of acetals **32** and **33** is likely of mechanistic significance (Scheme 6). The structure of these products was established by analytical data and NMR analysis. Especially diagnostic was the coupling constant between H_2 and H_3 ($J_{1,2}$ = 4.8 Hz), which indicates a *cis* relationship for these protons (C_3-stereochemistry was assigned at the precursor 7-oxonorbornene **7a** stage; cf. Scheme 5).[25] In addition, NOE experiments showed that isomer **32** has the formyloxy substituent attached to C_2. This was deduced by irradiation of the C_2-formyl proton (bold), which produced a significant enhancement for the signal due to H_2. No such relationship was found for **33**, which means in this case the formyloxy group must occupy the C_5-position. Although the C_5-configuration in **32** and **33** is less secure, the absence of NOE effects between H_2 and the C_5-substituents is consistent with the assigned *cis*-ring juncture.

Several experimental observations are also of interest: (1) The conversion of ozonide **25** to acetals **16a**, **32**, and **33** required *both* I_2 and $PhI(OAc)_2$ as oxidants, (2) the ratio of **32** and **33** was not significantly altered by added acetate or formate ion, (3) in no case did we observe the formation of diformyloxy derivatives corresponding to **16a**, and (4) the formation of diacetoxy compound **16a** was not stereoselective (mixture of at least two isomers). These data are consistent with a mechanism involving intramolecular transfer of a formyloxy group, as outlined in Scheme 6 for the major product **32**. We propose that initial β-cleavage of dialkoxy radical **26** occurs normally (cf. Figure 3), affording the tetrahydrofuran radical **27**.[22] At this point the reaction partitions along two pathways. One path (not shown) produces the diacetoxy compounds **16a**, via a second β-cleavage and oxidation of the resultant tetrahydrofuran diradical. This path is analogous to that postulated by Story and others (cf. **23** in Figure 3), involving a "simultaneous, or nearly simultaneous" β-scission.[22] Alternatively, radical **27** could undergo intramolecular cyclization to the more stable species **28**. Oxidation at this stage would ensure the migration of the formyloxy group to the α-face of the tetrahydrofuran ring. A number of possibilities exist for converting **28** to **32**. Since I_2 is required, radical abstraction of I could lead to **29**, which upon β-cleavage and fragmentation would produce the formyloxy radical **31**. Excellent precedent exists for each of these steps (CO is also a major product in the Story process, possibly

(25) For a similar example, see: (a) Bowden, B. F.; Coll, J. C.; Mitchell, S. J.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1980**, *33*, 2737. See also: (b) Jackman, L. M.; Sternhell, S. *Applications of N.M.R. Spectroscopy in Organic Chemistry*; Pergamon Press: Oxford, 1969.

formed by decomposition of formic anhydride).[22] Finally, addition of acetoxy radical from the α-face would afford the more stable *cis*-fused product **32**. An analogous mechanism, but involving initial cleavage of bond *b* in **26**, would lead to the regioisomeric bis-acetal **33**.

Further studies of this mechanism are in progress, and we expect that conversions of type **7a** → **32** might be of general use in natural product synthesis.

Experimental Section

***N*-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)-*N*-furan-2-ylmethylacetamide (12c).** A solution of 6.35 g (65.5 mmol) of furfurylamine (**4a**) and 18.2 mL (131 mmol) of Et_3N in 150 mL of CH_2Cl_2 was cooled to 0 °C, and treated with vigorous stirring with 15.0 g (65.5 mmol) of 5-chlorodibenzosuberane. After addition was complete, the reaction was stirred for an additional 30 min at 0 °C, and then at room temperature for 5 h before concentrating under reduced pressure. The residue, consisting of crude **4c**, was taken up in 13.4 g (131 mmol) of acetic anhydride and 15.9 mL (197 mmol) of pyridine. The reaction was then heated at 100 °C for 5 h, cooled to room temperature, and diluted with 100 mL of Et_2O. The resulting solution was washed with 20 mL each of 1 N NaOH, 1 N HCl, and saturated brine. After being dried over anhydrous $MgSO_4$, the organic layer was concentrated and the residue chromatographed (silica gel; pet ether/EtOAc, 5:1) to afford 21.80 g (93%) of **12c** as a crystalline solid: mp 90.0−0.5 °C (colorless crystals from Et_2O); IR (TCE) 2922, 1644, 1438 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 (s, 3H), 2.94−3.02 (m, 2H), 3.33−3.36 (m, 2H), 4.51 (s, 2H), 5.50 (br s, 1H), 6.14 (dd, J = 1.5 Hz, 2.1 Hz, 1H), 6.88 (br s, 1H), 7.10−7.20 (m, 7H), 7.40−7.43 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.2, 34.3 (2C), 44.3, 64.4, 107.1, 110.6, 126.5 (2C), 128.1 (2C), 130.3 (2C), 132.4, 137.4 (2C), 140.8 (2C), 141.7 (2C), 151.5, 171.9. Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.75; H, 6.40; N, 4.23.

3-Hydroxypent-4-enoic Acid (10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)furan-2-ylmethylamide (13c). A solution of 19.36 g (58.1 mmol) of **12c** in 100 mL of THF was cooled to −78 °C under Ar, and was treated dropwise, with vigorous stirring, with 43 mL (58.1 mmol) of 1.36 M lithium diisopropylamide/heptane/tetrahydrofuran/ethylbenzene.[6a] After addition was complete, the reaction was stirred at −78 °C for an additional 1 h, and was then treated in one portion with 7.7 mL (116.2 mmol) of acrolein. The resulting solution was stirred for 30 min at −78 °C, allowed to warm slowly to room temperature, and quenched with 50 mL of saturated NH_4Cl. After filtration, the aqueous layer was extracted with 4 × 50 mL of EtOAc, and the combined organic extracts were washed with 15 mL of saturated brine, dried over anhydrous $MgSO_4$, and concentrated to dryness under reduced pressure. Chromatography (silica gel, 5:1 pet ether/EtOAc) then afforded 21.03 g (93%) of **13c** as a colorless oil: IR (neat) 3433, 3056, 1733, 1633 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.50−2.70 (m, 2H), 2.93−3.06 (m, 2H), 3.25−3.37 (m, 2H), 4.37 (s, 1H), 4.51 (s, 2H), 4.59 (br s, 1H), 5.13 (dt, J = 1.5 Hz, 10.5 Hz, 1H), 5.30 (d, J = 16.5 Hz 1H), 5.49 (br s, 1H), 5.86 (ddd, J = 5.1 Hz, 10.5 Hz, 16.5 Hz, 1H), 6.12 (dd, J = 1.8 Hz, 3 Hz, 1H), 6.89 (br s, 1H), 7.10−7.25 (m, 7H), 7.35−7.43 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 34.3 (2C), 43.5, 69.5, 107.4, 110.6, 115.0, 126.6, 126.7, 128.3, 128.3, 130.4 (2C), 136.9 (2C), 136.9 (2C), 139.3 (2C), 140.7, 140.8, 141.9 (2C), 150.8, 173.8. HRMS(EI) calcd for ($C_{25}H_{25}NO_3$-H) ([M − H^+]) 386.1755; found 386.1758.

3-[3-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)-4-oxo-11-oxa-3-azatricyclo[6.2.1.0]undec-9-en-7-yl]propionic Acid, Methyl Ester (7c). A solution of 6.20 g (16.0 mmol) of **13c**, 9.9 mL (80 mmol) of trimethylorthoacetate (MOA), and 15 mL of toluene was thoroughly degassed with Ar, and was divided into three thick-walled reaction tubes containing a catalytic amount of pivalic acid and *tert*-butylcatechol. The tubes were sealed under Ar and heated with stirring at 130 °C for 90 h. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure, and the residue was chromatographed (silica gel, 4:1 pet ether/EtOAc) to give 5.08 g (72%) of **7c** as an amorphous solid: IR (neat) 3463, 1728, 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29−1.60 (m, 3H), 1.82−1.88 (m, 1H), 2.24−2.37 (m, 3H), 2.76 (dd, J = 5.1 Hz, 4.5 Hz, 1H), 3.01−3.06 (m, 2H), 3.25−3.34 (m, 2H), 3.38 (d, J = 14.4 Hz, 1H), 3.70 (s, 3H), 3.79 (d, J = 14.4 Hz, 1H), 4.76 (dd, J = 1.8 Hz, 4.5 Hz, 1H), 5.75 (d, J = 5.7 Hz, 1H), 6.24 (dd, J = 1.8 Hz, 5.7 Hz, 1H), 7.14−7.30 (m, 7H), 7.41−7.58 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.5, 33.2, 35.3, 35.5, 38.4, 43.4, 46.2, 47.0, 52.0, 62.1, 80.8, 87.3, 126.9, 127.0, 128.1, 128.1, 130.2, 130. 5, 132.2, 132.6, 134.7, 136.5, 137.1, 138.4, 141.5, 141.9, 171.3, 173.6 (restricted rotation of the dibenzosuberyl group leads to observance of all carbons). HRMS-(EI) calcd for ($C_{28}H_{29}NO_4$) ([M^+]) 443.2097; found 443.2104.

Also obtained from this reaction was 1.23 g (17%) of **6-[(10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)furan-2-ylmethylcarbamoyl]hex-4-enoic acid, methyl ester (6c)**: colorless oil; ^1H NMR ($CDCl_3$) δ 2.38 (m, 4H), 3.14 (d, J = 6.0 Hz, 2H), 2.93−3.35 (m, 4H), 3.69 (s, 3H), 4.50(s, 2H), 5.40−5.48 (m, 2H), 5.62−5.71 (m, 1H), 6.13 (dd, J = 1.5 Hz, 3.0 Hz, 1H), 6.84 (br s, 1H), 7.09−7.23 (m, 7H), 7.38−7.41 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.5, 34.4, 34.6, 38.9, 44.2, 52.2, 52.4, 107.6, 111.0, 111.2, 127.0 (2C), 128.6 (2C), 130.7 (2C), 132.1, 132.2, 132.9, 137.7 (2C), 141.2 (2C), 142.2 (2C), 151.9, 173.1, 174.2. HRMS(EI) calcd for ($C_{28}H_{29}NO_4$) ([M^+]) 443.2097; found 443.2094.

3-[4-Oxo-11-oxa-3-aza-tricyclo[6.2.1.0]undec-9-en-7-yl]propionic Acid, Methyl Ester (7a). A solution of 4.19 g (9.4 mmol) of **7c** and 1.02 g (9.4 mmol) of anisole in 5 mL of CH_2Cl_2 was cooled to 0 °C under Ar, and was treated dropwise with vigorous stirring with 5 mL of trifluoroacetic acid (TFA). After being stirred 1 h at 0 °C, the reaction mixture was allowed to warm to room temperature for 2 h, and was then concentrated to dryness under reduced pressure A small amount of residual TFA was removed by concentration from benzene. The residue was chromatographed (silica gel, 1:20 MeOH/EtOAc) to yield 2.07 g (88%) of **7a** as a colorless solid: mp 124.0−0.8 °C; IR (TCE) 3204, 3091, 1728, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.49−1.62 (m, 3H), 1.90−1.94 (m, 1H), 2.24−2.38 (m, 3H), 2.68 (dd, J = 5.4 Hz, 15.6 Hz, 1H), 3.71 (s, 3 H), 3.71 (dd, J = 1.8 Hz, 14.4 Hz, 1H), 3.92 (dd, J = 3.6 Hz, 14.4 Hz, 1H), 4.88 (dd, J = 1.5 Hz, 4.2 Hz, 1H), 6.35 (d, J = 5.7 Hz, 1H), 6.44 (dd, J = 1.5 Hz, 5.7 Hz, 1H), 6.48 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.6, 33.2, 37.1, 42.8, 44.3, 48.5, 52.0, 80.9, 86.0, 135.6, 138.0, 173.6, 174.1. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.12; H, 6.69; N, 5.58.

3-(2-Acetoxy-7a-formyloxy-5-oxooctahydrofuro[2,3-*c*]pyridin-3-yl)propionic Acid, Methyl Ester (32); 3-(7a-Acetoxy-2-formyloxy-5-oxooctahydrofuro[2,3-*c*]pyridin-3-yl)propionic Acid, Methyl Ester (33); 3-(2,7a-Diacetoxy-5-oxooctahydrofuro[2,3-*c*]pyridin-3-yl)propionic Acid, Methyl Ester (16a). A solution of 470 mg (1.87 mmol) of **7a** in 25 mL of CH_2Cl_2 was cooled to −78 °C, and was treated with a finely dispersed stream of O_3 until the blue color just persists. Excess O_3 was then removed by purging with O_2. The reaction mixture was allowed to warm to room temperature and was treated with vigorous stirring with 3.62 g (11.2 mmol) of iodosylbenzene diacetate and 1.90 g (7.48 mmol) of I_2 in one portion. The resulting dark solution was irradiated with stirring at room temperature for 4.5 h using a 200 W tungsten lamp. At the end of this period the reaction was treated dropwise with saturated aqueous $Na_2S_2O_3$ until the solution turned colorless. The resulting precipitate was filtered, and the aqueous phase was extracted with 5 × 20 mL of CH_2Cl_2. The combined organic extracts were washed with 10 mL of saturated brine, dried over anhydrous $MgSO_4$, and concentrated to dryness under reduced pressure. The residue was chromatographed (silica gel, EtOAc) to yield 400 mg (65%) of a mixture of **32**, **33**, and **16a**.[26] Further chromatography allowed separation into two components: **16a** and combined **32/33**.

Acetals **32** and **33** (yellow oils): ^1H NMR ($CDCl_3$) δ 1.88−1.94 (m, 2H), 2.11 (s, 3H), 2.14 (s, 1H), 2.38 (t, J = 7.5 Hz, 2H), 2.43 (t, J = 3 Hz, 1H), 2.71 (dd, J = 2.5 Hz, 5.5 Hz, 1H), 3.04 (d, J = 5.5 Hz, 1H), 3.69 (s, 3H), 3.71 (d, J = 5.5 Hz, 2H), 5.83 (br s, 1H), 6.43 (d, J = 4.8 Hz, 1H), 8.16 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.0, 23.0, 32.3, 33.8, 46.4, 47.2, 48.3, 52.2, 97.8, 112.0, 159.9, 170.0, 172.9, 173.0. HRMS (EI) calcd for ($C_{14}H_{19}NO_8$ + H) ([M + H^+]) 330.1189; found 330.1186.

16a (yellow oil): ^1H NMR ($CDCl_3$) δ 1.86−2.07 (m, 2H), 2.10−2.14 (m, 6H), 2.34−2.45 (m, 3 H), 2.70−2.80 (m, 2H), 3.03−3.09 (m, 1H), 3.48−3.70 (m, 2H), 3.72 (s, 3H), 6.31 (br s, 1H), 6.36 (d, J = 5.1 Hz, 1H); HRMS (FAB) Calcd for ($C_{15}H_{21}NO_8$ + H) [(M + H^+)] 344.1345; found 344.1346.

(26) Comparable yields were obtained on 2−3 g scales (not optimized).

3-(5-Oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*c*]pyridin-3-yl)propionic Acid, Methyl Ester (3a). A total of 395 mg (1.20 mmol) of a mixture of **32**, **33**, and **16a**, prepared as described above was dissolved in 4 mL of acetic acid and was treated with vigorous stirring with a solution of 1.85 g (24.0 mmol) of NH_4OAc in 4 mL of H_2O. The reaction was then warmed in an oil bath maintained at 55 °C for 8 h. At the end of this period the reaction was concentrated under reduced pressure and the residue was taken up in 2 mL of CH_2Cl_2 and adsorbed on ~1 g of silica gel. After drying, the solid was applied to the top of a short silica gel column and chromatographed (1:9 MeOH/CH_2Cl_2) to give 130 mg (49%) of **3a** as an off-white solid.. Recrystallization from MeOH afforded **3a** as a white powder, decomposing slowly above 220 °C (open capillary): IR (TCE) 3204, 1740, 1694, 1644, 1610 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.50−2.57 (m, 4H), 3.16 (t, J = 3.3 Hz, 2H), 3.60 (s, 3H), 4.27 (d, J = 2.1 Hz, 2H), 6.48 (d, J = 2.4 Hz, 1H), 7.71(s, 1H), 10.32 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.0, 29.7, 35.2, 51.9, 111.3, 115.9, 118.5, 120.6, 170.2, 173.8 (1 C superimposed on DMSO-d_6). Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.61. Found: C, 59.42; H, 6.29; N, 12.61.

3-(5-Aminomethyl-4-carboxymethyl-1*H*-pyrrol-3-yl)propionic Acid (1) (Porphobilinogen). A solution of 130 mg (0.59 mmol) of lactam **3a** in 1.5 mL of 2 N KOH was stirred at room temperature with protection from light for 96 h. The reaction was then adjusted to pH 6 with 40% HOAc, and allowed to stand until precipitation appeared complete. The resulting solid was collected by filtration, washed with 0.5 mL of ice-cold MeOH, and dried overnight under vacuum to afford 78 mg (59%) of **1** as a colorless solid, decomposing slowly above 160 °C (open capillary), and having identical chromatographic and spectral properties as an authentic sample (lit.[1h] yield 67%): IR (TCE) 3272, 3148, 3058, 1706, 1514 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.37−2.42 (m, 2H), 2.55−2.60 (m, 2H), 3.11 (s, 2H), 3.85 (s, 2H), 6.43 (s, 1H), 10.58 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.9, 35.4, 36.1, 36.8, 115.0, 118.8, 122.7, 123.3, 175.8, 175.9. Anal. Calcd for $C_{10}H_{14}N_2O_4 \cdot H_2O$: C, 49.17; H, 6.60; N, 11.47. Found: C, 49.61; H, 6.43; N, 11.59.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for **1**, **3a**, **6c**, **7a**, **7c**, **12c**, **13c**, **16a**, **32**, and **33** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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