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Exploring Symmetry-Based Logic for a Synthesis of Palau'amine

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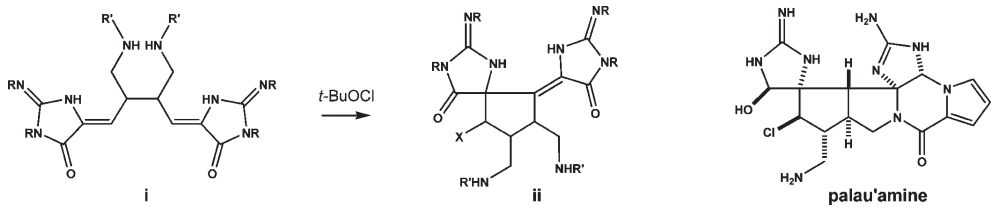

A synthetic approach to palau'amine is described that exploits veiled symmetry in the structure. Bis-alkylidenes **i** have been prepared and found susceptible to halogenative desymmetrization using *t*-BuOCl. This oxidation forms the imbedded spirocyclopentane motif observed in the natural product. A host of atypical reactions and processes developed during these studies are discussed, as are plans for completing total syntheses of this compound class.

Introduction

Palau'amine (**1**, Figure 1)[1] is a prominent member of the pyrrole/imidazole family of marine derived alkaloids, a group whose numbers continue to grow with research on selected pacific sponges. Relationships within the group have been discussed extensively, relating mainly to proposals for unified biosynthetic schemes.[1b,2] While direct evidence is lacking, an early consensus viewed the class as originating with 3-amino-1-(2-aminoimidazolyl)prop-1-ene (**2**).[3] One can trace this motif in scores of natural products described throughout four decades of literature. In this scenario, aminoimidazole **2** and pyrrole-2-carboxylic acid are constituents of oroidin,[4] itself the feedstock from which the larger family derives—perhaps wherein genes encoding enzymatic machinery manipulating intermediates have transferred and evolved across producing species.[2a] An alternate view stems from Al-Mourabit's recent insightful work on autoxidative incorporation of guanidine into partially oxidized proline dimers.[5] This direct access to displacamides from a non oroidin source adds another dimension to biosynthesis considerations.

Origins notwithstanding, palau'amine and its relatives harbor two units of aminoimidazole **2**. It is these dimeric conjugates that make up the most structurally and biochemically interesting members of the set. Palau'amine was isolated as an antifungal constituent of *S. aurantium*.[1] The substance was also reported to possess antimicrobial activity and to inhibit stimulated human T-cell proliferation in vitro, while being relatively innocuous to resting lymphocytes. To date these functions have not been examined further or characterized at a molecular level. Actually, the same is true of the various biological effects attributed to other palau'amine type bis-guanidines. The stalemate derives from a scarcity of the materials in nature and the fact that assembling related structures in the laboratory has proven an unusually difficult problem.

The imbedded cyclopentane scaffolding the two guanidine units within **1** is its signature feature. Installing this motif

(1) (a) Kinnel, R. B.; Gehrken, H.-P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376–3377. (b) Kinnel, R. B.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281–3286.

(2) (a) Al-Mourabit, P., Potier *Eur. J. Org. Chem.* **2001**, 237–243. (b) Baran, P. S.; O'Malley, D. P.; Zografos, A. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 2674–2677. (c) Grube, A.; Immel, S.; Baran, P. S.; Köck, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 6721–6724.

(3) Wright, A. E.; Chiles, S. A.; Cross, S. S. *J. Nat. Prod.* **1991**, *54*, 1684–1686.

(4) (a) Garcia, E. E.; Benjamin, L. E.; Fryer, R. I. *J. Chem. Soc., Chem. Commun.* **1973**, 78–79. (b) Gautschi, J. T.; Whitman, S.; Holman, T. R.; Crews, P. *J. Nat. Prd.* **2004**, *67*, 1256–1261.

(5) (a) Ravert, N.; Al-Mourabit, A. *J. Am. Chem. Soc.* **2004**, *126*, 10252–10253. (b) Vergne, C.; Boury-Esnault, N.; Perez, T.; Martin, M.-T.; Adeline, M.-T.; Dau, E. T. H.; Al-Mourabit, A. *Org. Lett.* **2006**, *8*, 2421–2424. (c) Vergne, C.; Appenzeller, J.; Ratinaud, C.; Martin, M.-T.; Debitus, C.; Zaparucha, A.; Al-Mourabit, A. *Org. Lett.* **2008**, *10*, 493–496.

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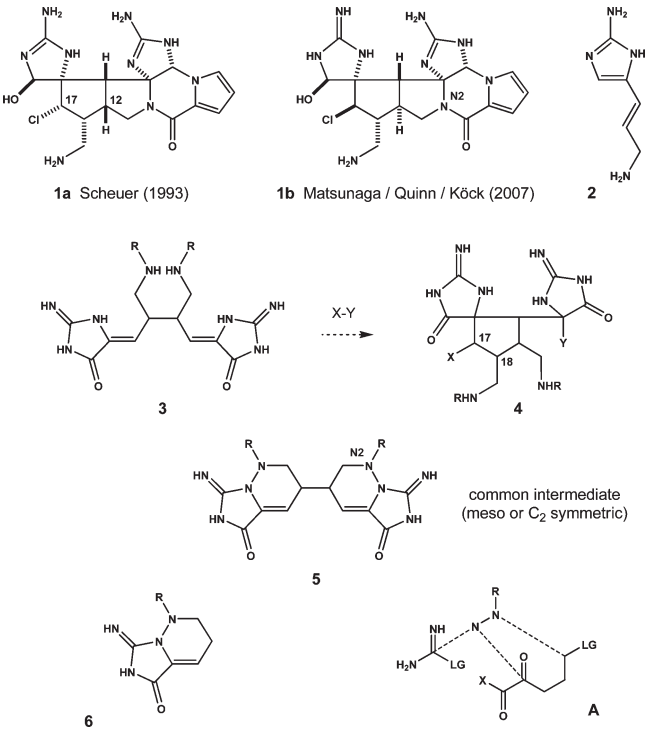


FIGURE 1. Original and revised palau'amine structures. In either case, the imbedded spirocyclopentane motif can be viewed as a product of halogenative desymmetrization.

becomes de facto the central event in any projected synthesis. Several laboratories have published creative models on the topic and tactics range from putatively biomimetic to decidedly abiotic.[6] Overman's beautiful work in the area has reached an advanced stage.[7] Baran et al. have recently reported the first synthesis of axinellamines and massadines—truly seminal achievements.[8a,8b] Our own experiments fall in the biomimetic vein wherein we view the carbocycle in **1** as derivative of oxidative halogenation; in particular of *seco*-bis-alkylidenes **3**.[9] This choice makes symmetry in the problem clear, provides options for varying diastereochemical outcomes and, assuming **4** to be a viable intermediate en route to **1**, reduces the initial task to that of controllably dimerizing a dispacamide alkaloid.[5b] We targeted fused heterobicycle **6** as a dispacamide synthon for this purpose, such that dimerization could occur via a derived dienolate oxidation. We describe here methods to synthesize the requisite monomers and show their dimerization can be uniquely executed in both a regio- and stereocontrolled manner. We further demonstrate that derived bis-alkylidenes **3** are in fact susceptible to halogenative spirocyclization, validating our blueprint for syntheses of palau'amine type alkaloids generally.

Results and Discussion

The ring system in **6** had not been synthesized previously, although a generic relationship to simpler components was apparent (Figure 1). The Claisen condensation product of γ-butyrolactone and $(CO_2Et)_2$ was degraded with HBr/AcOH and the crude reaction treated with MeOH/cat. H_2SO_4 to afford brominated α-keto ester **7** (Scheme 1).[10] This material was exposed to hydrazine to generate a tetrahydropyridazine carboxylate[11] that was subsequently allylated and saponified to afford **8**. When carboxylic acid **8** was condensed with *o*-xylyldiamine-derived methylisothiourea **9**,[12] the adduct (**10**) could be induced to cyclize in situ by concentrating the reaction mixture at 70 °C in vacuo. This served to generate the desired *N*-aminoglycocyamidine **11** via net extrusion of methyl mercaptan.

With **11** in hand, we set out to dimerize the material using enolate oxidation techniques.[13] Enamide **11** could be deprotonated readily at low temperature with KHMDS. The resultant dienolate was prone to oxygenation,[14] but if anaerobic conditions were established, addition of $FeCl_2(DMF)_3FeCl_4$[15] generated dimeric products efficiently. With the original assignment of palau'amine stereochemistry[1,16] (namely, **1a**)

(6) For reviews, see: (a) Köck, M.; Grube, A.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 6586–6594. (b) Jacquot, D. E. N.; Lindel, T. *Curr. Org. Chem.* **2005**, *9*, 1551–1565. For recent contributions, see: (c) Namba, K.; Kaihara, Y.; Imagawa, I.; Tanino, K.; Williams, R. M.; Nishizawa, M. *Chem.—Eur. J.* **2009**, *15*, 6560–6563. (d) Hudon, J.; Cernak, T. A.; Ashenhurst, J. A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 8885–8888. (e) Cernak, T. A.; Gleason, J. L. *J. Org. Chem.* **2008**, *73*, 102–110. (f) Bultman, M. S.; Ma, J.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 6821–6824. (g) Zancanella, M. A.; Romo, D. *Org. Lett.* **2008**, *10*, 3685–3688. (h) Wang, S.; Romo, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1284–1286. (i) Sivappa, R.; Hernandez, N. M.; He, Y.; Lovely, C. J. *Org. Lett.* **2007**, *9*, 3861–3864. (j) Spoering, R. M. Studies Toward a Synthesis of Palau'amine. Ph.D Thesis, Harvard University, **2005.**

(7) Lanman, B. A.; Overman, L. E.; Paulini, R.; White, N. S. *J. Am. Chem. Soc.* **2007**, *129*, 12896–12900 and references cited therein .

(8) (a) O'Malley, D. P.; Yamaguchi, J.; Young, I. S.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3581–3583. (b) Su, S.; Seiple, I. B.; Young, I. S.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 16490–16491.

(9) Garrido-Hernandez, H.; Nakadai, M.; Vimolratana, M.; Li, Q.; Doundoulakis, T.; Harran, P. G. *Angew. Chem., Int. Ed.* **2005**, *117*, 765–769.

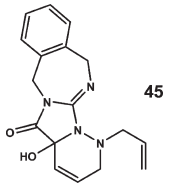
(10) Ohler, E.; Schmidt, U. *Chem. Ber.* **1975**, 2907–2916.

(11) Broger, E. M.; Crameri, Y.; Imfeld, M.; Montavon, F.; Widmer, R. *Eur. Pat. Appl.* 1993, EP 570764.

(12) (a) Kawahara, S.; Uchimaru, T. *Z. Naturforsch., B: Chem Sci.* **2000**, *55*, 985–987. (b) Elslager, E. F.; Worth, D. F.; Haley, N. F.; Perricone, S. C. *J. Heterocycl. Chem.* **1968**, *5*, 609–612.

(13) (a) Kauffmann, T.; Neissner, G.; Köppelmann, B. E.; Legler, J.; Schönfelder, M. *Angew. Chem., Int. Ed.* **1968**, *7*, 540–541. (b) Ito, Y.; Konoike, T.; Harada, T.; Seagusa, T. *J. Am. Chem. Soc.* **1977**, *99*, 1487–1493. (c) Renaud, P.; Fox, M. A. *J. Org. Chem.* **1988**, *53*, 3745–3752. (d) Porter, N. A.; Su, Q.; Harp, J. J.; Rosenstein, I. J.; MaPhail, A. T. *Tetrahedron Lett.* **1993**, *34*, 4457–4460. (e) Schmittel, M. *Top. Curr. Chem.* **1994**, 183–230. (f) Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857–12869.

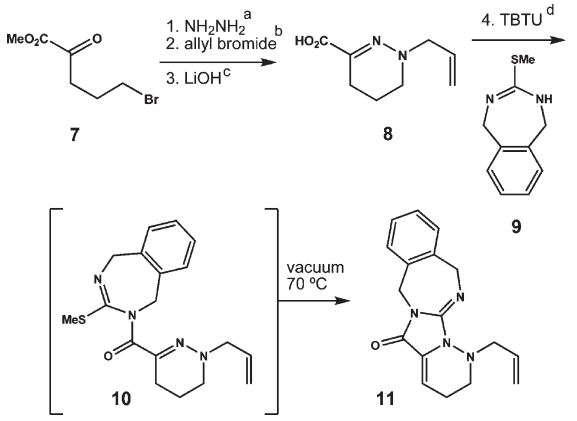
(14) The yield of dimeric products in nondeoxygenated solvents is lowered due to competing formation of angularly hydroxylated monomer **45**. Compound **45** also forms (75% yield) when **11** is treated with KHMDS alone (1.1 equiv, −78 °C, 0.2M, 1 h) in nondeoxygenated THF. Compound **45** presumably derives from a corresponding hydroperoxide which is either reduced in situ or hydrolyzed during isolation.



(15) Tobinaga, S.; Kotani, E. *J. Am. Chem. Soc.* **1972**, *94*, 309–310.

(16) Recent evidence suggests Scheuer and Kinnel's assignment of palau'amine relative stereochemistry (ref 1) is likely incorrect. Characterization of newly isolated relatives implies natural palau'amine is configured as drawn in **1b**. For details, see: (a) Kobayashi, H.; Kitamura, K.; Nagai, K.; Nakao, Y.; Fusetani, N.; van Soest, R. W. M.; Matsunaga, S. *Tetrahedron Lett.* **2007**, *48*, 2127–2129. (b) Buchanan, M. S.; Carroll, A. R.; Addepalli, R.; Avery, V. M.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem.* **2007**, *72*, 2309–2317. (c) Grube, A.; Köck, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2320–2324. Overman's (ref 7) and Baran's (ref 8) synthetic studies further support these arguments.

SCHEME 1[a]



[a]Reaction conditions: (a) 1 equiv of NH_2NH_2,10 equiv of AcOH, MeOH/H_2O, rt to 62 °C (>95%); (b) 1 equiv of KHMDS; 1.2 equiv of allyl bromide, THF, −35 °C (90%); (c) 1.5 equiv of LiOH, 2:1:1 THF/MeOH/H_2O; aq citric acid (>95%); (d) 1.1 equiv of **9**, 1 equiv of TBTU, 3 equiv of $(i\text{-Pr})_2$NEt, DMF, then concentrates in vacuo at 70 °C (72%). TBTU = 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate.

in mind, the desired outcome was a *meso* dimer resulting from homocoupling at the γ position of monomer **11** (namely **14a**, Scheme 2). However, little of that material was formed. Rather, we obtained predominately a diastereomeric mixture of α,γ adducts **12** along with lesser amounts of α,α regioisomer **13**.[17] The trace amount of **14** observed was present as a 1:1 mixture of *meso* and C_2 forms.[18] We subsequently found that α,α coupling product **13** was unstable and rearranged to α,γ forms **12** in toluene solution at 85 °C.[19] Rather than disproportionate or Cope rearrange to γ,γ isomers **14**, the molecule undergoes a net 1,3-sigmatropic shift. It was possible to purify **13** and photolyze the compound to generate additional **14**, although this protocol was inefficient and continued to afford substantial amounts of **12**. This result, and the fact we were unable to independently convert **12** to its γ,γ counterparts **14**,[20] necessitated that attention turn to controlling kinetic selectivity in the oxidative dimerization itself.

We observed that substituting I_2 for $FeCl_2(DMF)_3FeCl_4$ as the oxidant (Scheme 2) provided for a similarly efficient dimerization, although **14** was no longer detectable in the crude reaction mixture and the ratio of dimeric products now favored isomers **13**. This was interpreted in terms of a monomeric radical dimerizing through an early, reactant-like transition state.[13c,21] Independently, $FeCl_2(DMF)_3FeCl_4$ was found not to convert **13** into **14** in THF solution at rt.[22]

It therefore seemed reasonable to infer the Fe(III)-based procedure (entry 1) involved an organometallic species whose homocoupling was more responsive to ground-state stability of incipient products. If true, furthering that trend could make the γ,γ outcome competitive, perhaps favored, provided regioisomers **14** were indeed lower in relative energy.[23] Replacing Fe(III) with Cu(II) did increase the proportion of **14** formed (entry 3), although the reaction remained impractical for preparative purposes. The breakthrough came when the potassium dienolate was treated with an equivalent of Cp_2TiCl_2 prior to oxidation. In that case, we obtained largely desired regioisomers **14** in good yield (Scheme 3). When $(i\text{-PrCp})_2TiCl_2$ was used, selectivity for **14** was essentially complete; regioisomers **12** or **13** could no longer be detected in crude reaction mixtures. Our understanding of the mechanism operating is limited. However, reasoning by analogy to Schmittel's findings on the electrochemical oxidation of simpler titanocene enolates,[24] we interpret the outcome in terms of Cu(II) engaging an intermediate of type **15** to initiate dimerization via an electron-deficient species whose Ti−O bond is intact at the point of C−C bond formation.[25] This would effectively block the dienolate α position. Attempts to further characterize details of this atypical oxidative coupling are ongoing.

Our initial plans for palau'amine synthesis called for removing one allyl unit from *meso*-**14** en route to a substance carrying the acylpyrrole unit on N2 (see Figure 1) needed to construct the dipyrrolopyrazinone motif found in **1** (vide infra). Unfortunately, the seemingly simple task of deallylating **14a**/**b** proved untenable, at least by direct means.[26] Thus, a more ambitious goal was pursued wherein the acylpyrrole component would be installed early and carried through the synthesis, giving our dimeric intermediates the bis-pyrrole composition common to axinellamine, massadine, carteramine, and konbu'acidin.[6,16] The monomer

(17) A single diasteromer of **12**, the *dl* form of **13**, **21-*meso***, polycycle **29**, and reduction products **33b** have been characterized by X-ray crystallography. See the Supporting Information for details.

(18) *Meso* and racemic C_2 forms **14a**/**14b** are inseparable by silica gel chromatography. Ratios are determined by ^{1}H NMR and HPLC analyses (Chiralcel-OD-H, isocratic: 80% *i*-PrOH/hexanes).

(19) $T^{1/2}$ for the conversion **13** → **12** in toluene solution at 85 °C is 56 min ($E_a \sim 27$ kcal/mol).

(20) Attempts to establish equilibrium between **12** and **14**, which would presumably favor **14** for steric reasons, failed. Such experiments included thermolyses, acid (Lewis and Bronstead) treatments, and exposure to catalysts intended to generate ion-paired metal π-allyl intermediates.

(21) Ziegler, F. E.; Harran, P. G. *J. Org. Chem.* **1993**, *58*, 2768–2773.

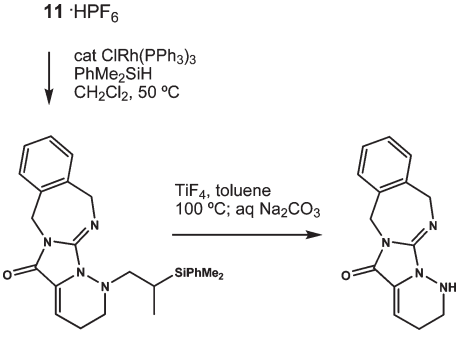
(22) A 0.1 M THF solution of **13** is unchanged at room temperature after 2 h in the presence of 0.6 equiv of $FeCl_2(DMF)_3FeCl_4$.

(23) This statement reflects a corollary to the Hammond postulate. However, available data do not confirm kinetic control nor have we determined that "homocoupling" is, in fact, mechanistically accurate. The heterogeneous nature of the reactions complicates in situ observations. We speculate only to convey reasoning as our experiments progressed.

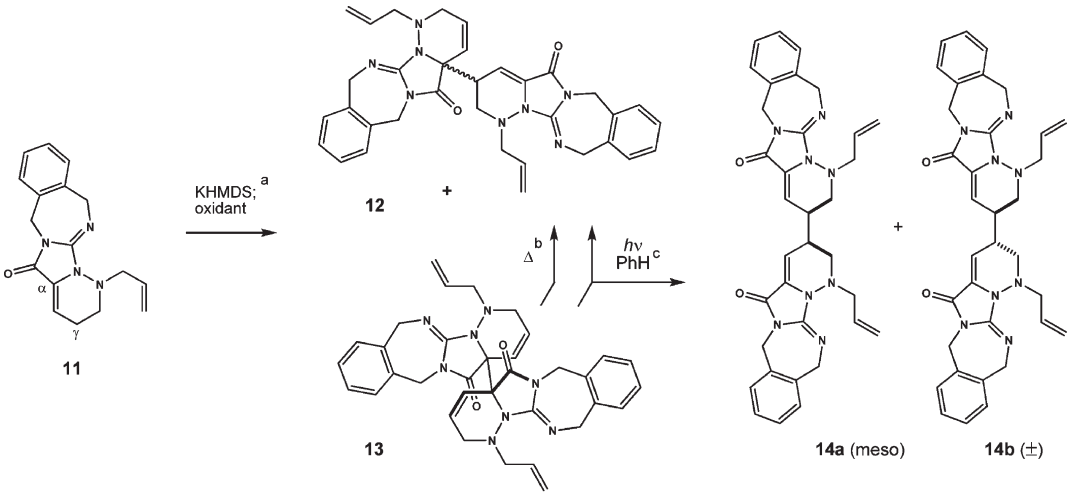
(24) (a) Schmittel, M.; Söllner, R. *Chem. Ber.* **1997**, 771–777. (b) Schmittel, M.; Burghart, A.; Malisch, W.; Reising, J.; Söllner, R. *J. Org. Chem.* **1998**, *63*, 396–400.

(25) This may not be the case in oxidations involving $FeCl_2(DMF)_3FeCl_4$, wherein significant amounts of α,γ-regioisomeric dimers are consistently observed (Schemes 2 and 5).

(26) The hydrohexafluorophosphate salt of **11** could be deallylated using the two-step sequence shown below. Unfortunately, these methods proved neither an efficient nor selective means to deprotect **14**.



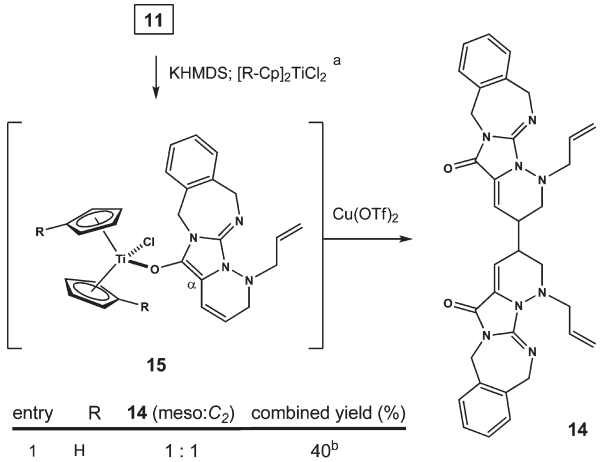
SCHEME 2[a]



entry	oxidant	12[d]:13[e]:14[f]	combined yield (%)
1	$FeCl_2(DMF)_3 \cdot FeCl_4$	5.4 : 1.0 : 1.0	80
2	I_2	1.0 : 2.0 : --	71
3	$Cu(OTf)_2$	1.5 : 1.0 : 1.0	84

[a]Reaction conditions: (a) 1.05 equiv of KHMDS, degassed THF, −78 °C, 30 min; add 1.1 equiv of oxidant and stir for 1 h at −78 °C; (b) 0.02 M **13** in degassed toluene, 95 °C, 1 h (81%); (c) *hν* (Rayonet, 254 nm bulb set), 0.01 M in deoxygenated PhH, 2 h (36% **12** + 20% **14a/b**); (d) **12** isolated as ∼1:1 mixture of diastereomers; (e) only *dl* form observed (ref 18); (f) **14** isolated as an equal mixture of *meso* amd racemic C_2 forms.

SCHEME 3[a]



entry	R	14 (meso:C_2)	combined yield (%)
1	H	1 : 1	40[b]
2	$CHMe_2$	2 : 1	81

[a]Reaction conditions: (a) KHMDS (1.1 equiv), deoxygenated THF, −78 °C, 30 min; then $(R\text{-}Cp)_2TiCl_2$ (1.15 equiv), −78 °C, 3 h; then $Cu(OTf)_2$ (1.6 equiv), −78 °C, 3.5 h; (b) 20% yield of **12** and 10% recovered **11** isolated in this experiment.

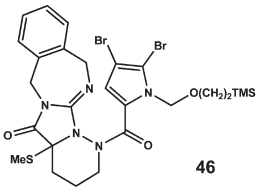
required for this purpose was synthesized beginning with tetrahydropyridazine **16** (Scheme 4). This material was treated with acid chloride **17**[27] and the adduct saponified to afford carboxylic acid **18**. Condensation with methylisothiourea **9** subsequently provided amide **19** from which target **20** was derived by mild thermolysis in the presence of $HgCl_2$.[28]

The potassium dienolate of **20** decomposed readily at −78 °C. However, if **20** was treated with $(i\text{-}PrCp)_2TiCl_2$ prior to KHMDS, subsequent oxidation with $Cu(OTf)_2$ afforded dimers **21** (3.3:1 *meso*/C_2) in respectable yield (Scheme 5). Notably, changing the oxidant to $FeCl_2(DMF)_3FeCl_4$ reversed the selectivity to now favor the C_2 isomer (1:3 *meso*/C_2). The yield in this case was diminished due to competing formation of α,γ regioisomeric dimers. Nonetheless, selectivity and efficiency observed were encouraging given the complexity of the construction.

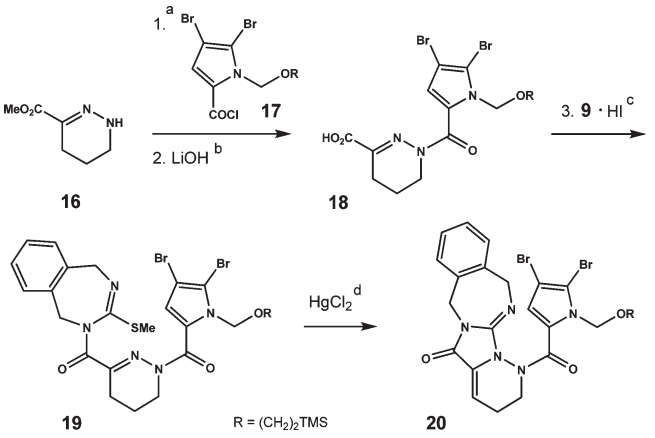
With *meso*-**21** assembled, we again faced a desymmetrization, yet one quite different than confronted in **14**. Plans called for saturating a single N−N σ bond en route to a compound of type **24** (Scheme 6A). Models suggested relieving one such ring constraint would provide flexibility necessary for the intended spirocyclization (as drawn), while the N−N bond remaining would enforce a *syn* relationship between the C−Cl bond and C18 aminomethyl branch within polycycle **25** generated upon chlorination. Of course, this outcome would require chemoselective halogenation of the vinyl hydrazide in **24**, itself a tenuous proposal. However, the alternative was to delay desymmetrization and break both N−N bonds in **21** en route to bis-alkylidenes of type **3** (Figure 1). The concern there was that stacked conformers having minimal allylic strain in the tether connecting glycocyamidine units would react preferentially to give products having a *trans* relationship between ring substituents at

(27) Katz, J. D.; Overman, L. E. *Tetrahedron* **2004**, *60*, 9559–9568.

(28) The use of substoichiometric amounts of $HgCl_2$ in the reaction leads to isolation of angular thioether **46**. This material can be converted independently to **20** by re-exposure to $HgCl_2$/pyr (CH_3CN, 70 °C).



SCHEME 4[a]

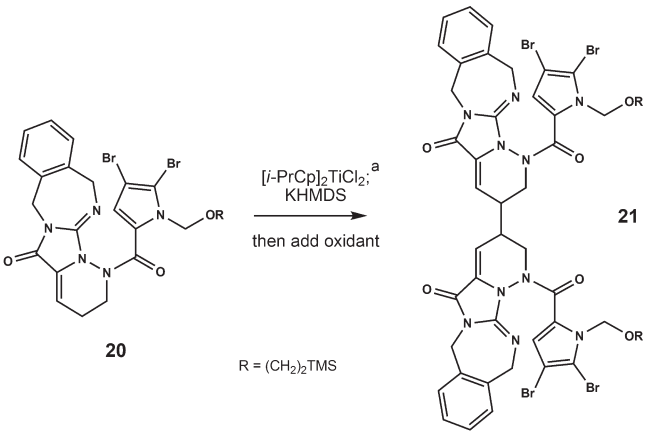


[a]Reaction conditions: (a) 0.95 equiv of **17**, pyr, CH_3CN, rt (94%); (b) LiOH, 1:1 THF/H_2O, 0 °C (95%), recrystallized; (c) 1.05 equiv of **9**, HI, 1.1 equiv of TBTU, 3 equiv of $(i\text{-Pr})_2NEt$, DMF, rt (>95%); (d) 1.5 equiv of $HgCl_2$, 3 equiv of pyr, CH_3CN, reflux 3 h (70%).

carbons 17 and 18. This was unacceptable in light of Scheuer's original palau'amine assignment (**1a**) and, thus, means to generate structures **24** took priority.

A two-electron reduction of **21** having the effect of saturating one N−N bond was an interesting problem. We chose to pursue a conjugate addition manifold, the thought being hydride addition to one enamide could generate a transient ketene aminal (e.g., **22**) perhaps able to β-eliminate, wherein the ring-opened product (**23**) would tautomerize upon protonation to give **24**. In practice, working with *meso*-**21**, procedures employing various soft metal hydrides, either as isolated reagents or generated in situ, were ineffective for this purpose. However, we did observe that Wilkinson's complex could catalyze partial reduction of **21** to afford **27** in the presence of $PhMe_2SiH$,[29] provided that **21** was pretreated with 2 equiv of NH_4PF_6 to suppress catalyst poisoning. Isolated yields were at first poor, although the method was improved significantly using rhodium carbenoid **31**[30] complexed with Buchwald's "DavePhos"[31] as catalyst. This procedure gave **27** in yields indicative of multiple catalyst turnovers. The next question was whether the silylketene aminal putatively formed in situ (namely **26**) could be coaxed to fragment en route to a structure of type **24**. Fluoride treatment of crude hydrosilylation mixtures decreased the isolated yield of **27**, but not productively. We presumed the NH_4PF_6 pretreatment used to facilitate conversion had converted *meso*-**21** into a salt form wherein **26** would be protonated and could self-immolate in situ. Lewis acids, rather than NH_4PF_6, were therefore screened as alternate promoters. When $MgBr_2$ etherate was employed, we continued to isolate **27**, but the major product proved to be a single diastereomer of polycycle **28**, an outcome rationalized in terms of a Lewis acid-coordinated form of **26** undergoing an internal Mukaiyama−Michael addition. This unintended result was potentially valuable. The core diazabicycle in **28** was identical to that targeted in **25**, just

SCHEME 5[a]



entry	oxidant	**21** (meso:C_2)	combined yield (%)
1	$FeCl_2(DMF)_3 \cdot FeCl_4$	1 : 3	62[b]
2	$Cu(OTf)_2$	3.3: 1	64

[a]Reaction conditions: (a) $(i\text{-PrCp})_2TiCl_2$ (1.15 equiv), deoxygenated THF, 0 to −78 °C, 30 min; then KHMDS (1.1 equiv), −78 °C, 1.5 h; then $Cu(OTf)_2$ (1.5 equiv) or $FeCl_2(DMF)_3FeCl_4$ (1 equiv), 3 h, −78 °C to rt, 1.5 h; (b) 20% yield of α,γ dimers (analogous to **12**) are isolated in this experiment. *meso*-**21** has been characterized by X-ray crystallography (ref 17).

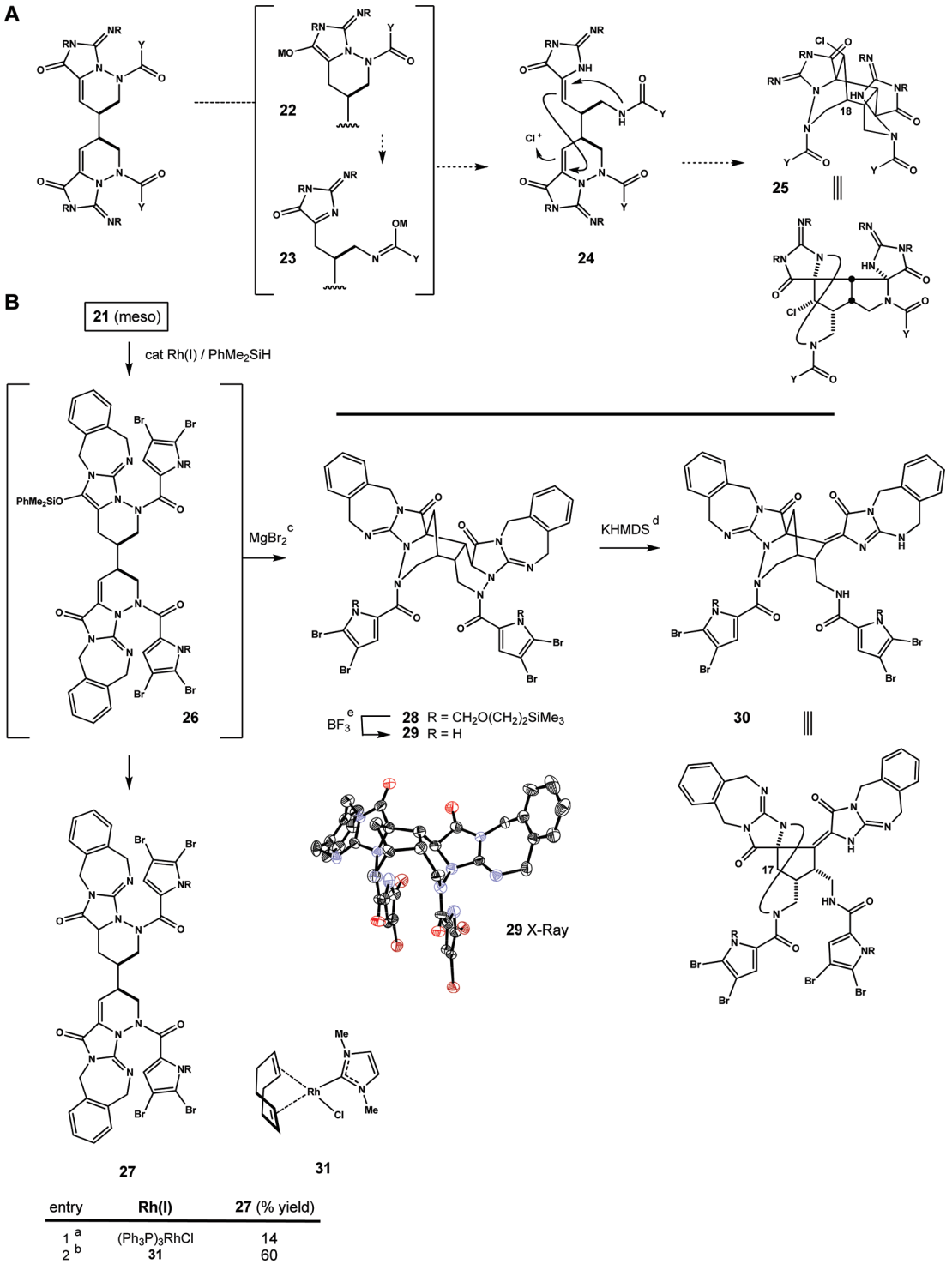
lacking halogen on the methano bridge. X-ray diffraction analysis of crystals grown from samples of SEM-deprotected **28** showed the desired relative stereochemistry throughout the structure. Moreover, treating **28** with KHMDS efficiently cleaved the hydrazide N−N bond adjacent to the enolizable methine to afford **30**. Rendering that material more like we draw the natural product (as shown) makes its relation to the original palau'amine assignment clear. One could envision scenarios in which a series of controlled reductions might achieve that end.

With that topic left for a future date, we returned to the issue of generating **24**. We were unable to steer the hydrosilylation of *meso*-**21** toward **24** in situ, yet the observation that **28** cleanly fragmented to **30**, presumably via its potassium enolate, upon KHMDS treatment suggested the **22** → **23** conversion was viable, despite the N−N bond to be cleaved being oriented near orthogonal to the enolate π system. We thus treated isolated **27** with KHMDS. Unlike **28**, this caused extensive decomposition. However, if we dissolved **27** in DMF and added 1 equiv of anhydrous LiCl, followed by DBU,[32] we could isolate a ring-opened material in good yield. Unfortunately, ring-opening occurred cleanly within the oxidized "half" to afford extended chromophore **32** as a canary yellow solid (Scheme 7).

Enolizing a monoreduced dimer was evidently not a method to accesss **24**. While paths to circumvent the problem seemed available, our next move was actually dictated by external events. In early 2007, a succession of papers called into question Scheuer's original assignment of palau'amine relative stereochemistry.[16] Characterization of newly discovered relatives, along with reinterpretation of spectroscopic data collected on palau'amine itself, suggested the molecule was epimeric at carbons 12 and 17, wherein **1b** (Figure 1)

(29) Ojima, I.; Kogure, T.; Nagai, Y. *Tetrahedron Lett*. **1972**, 5035.
(30) Voutchkova, A. M.; Appelhans, L. N.; Chianese, A. R.; Crabtree, R. H. *J. Am. Chem. Soc*. **2005**, *127*, 17624–17625.
(31) Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed*. **2005**, *44*, 6173–6177.
(32) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett*. **1984**, *25*, 2183–2186.

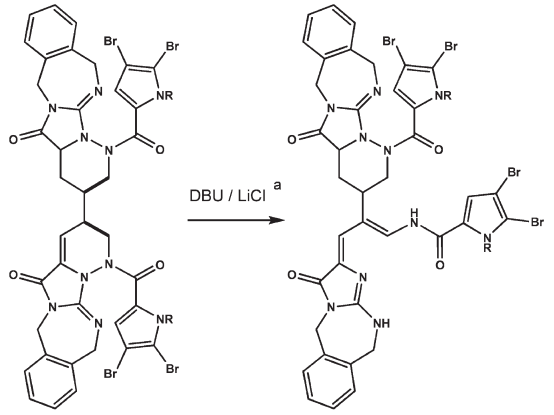
SCHEME 6. (A) Initial Strategy To Parlay Dimers **21** into Palau'amine Intermediates with Control of Relative Stereochemistry. (B) Additional Synthetic Routes[a]



[a]Reaction conditions: (a) NH_4PF_6 pretreatment; 20 mol % of $(Ph_3P)_3RhCl$, $PhMe_2SiH$ (1.1 equiv), CH_2Cl_2, 45 °C, 24 h; (b) NH_4PF_6 pretreatment; 5 mol % of **31**, 5 mol % of 2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl, $PhMe_2SiH$ (1.1 equiv), MgI_2 (0.8 equiv), CH_2Cl_2, 45 °C, 18 h (60% **27** + 11% **28**); (c) same as (b) except NH_4PF_6 treatment omitted and $MgBr_2 \cdot Et_2O$ (1.5 equiv) used in place of MgI_2 (45% **28** + 30% **27**); (d) KHMDS (2.1 equiv), THF, −78 °C to rt, 1 h, 85%; (e) $BF_3 \cdot Et_2O$ (5 equiv), CH_2Cl_2, 0 °C to rt, 3.5 h; satd $NaHCO_3$, 80%. X-ray structure of **29** shown in ORTEP format (30% probability thermal ellipsoids, hydrogen atoms omitted for clarity).

would be the true form of the natural product. Diastereomer **1b** was a fascinating variant and fortunately, one of numerous potential stereochemical outcomes downstream of a **3** → **4** oxidation (Figure 1). Up to this point, we had targeted **24** as a halogenation substrate intending to enforce an "all syn" substituent array about the cyclopentane core as

SCHEME 7[a]



[a]Reaction conditions: (a) 1.3 equiv of DBU, 1.2 equiv of LiCl, DMF, 50 °C, 3 h (70%).

assigned in **1a**. If **1b** were the natural product, the N−N bond in **24** would be an unnecessary constraint and we could simply target symmetric bis-alkylidenes **3** as per the generic plan.

This was examined first in the *meso* series. Altering the stoichiometry of silane to 2.2 equiv and using a combination of NH_4PF_6 and MgI_2 additives, rhodium-catalyzed reduction of *meso*-**21** provided doubly saturated compounds **33** in high yield (Scheme 8). All three possible stereoisomers were formed—two *meso* forms **33a**/**b** along with nonsymmetric material **33c**. This was of no preparative consequence. After careful experimentation, we found the isomeric mixture could be treated with excess Cy_2BOTf followed by brief exposure to KHMDS to afford doubly ring-opened bis-alkylidene **34** in good yield. The reaction generates a mixture of geometric isomers upon hydrolytic workup; however, these converge to a single, symmetric form during silica gel chromatography or standing in chloroform solution at room temperature. We tentatively assign *Z* stereochemistry at both alkenes in **34**.[33]

With **34** in hand, we could examine the central tenant in our approach—the propensity of such compounds to form spirocyclic products upon oxidative halogenation. Gratifyingly, when **34** was dissolved in THF containing $MgCl_2$, cooled to −78 °C, and treated with freshly prepared *t*-BuOCl, we obtained three chlorinated products, and all data suggests they contain the target spirocyclopentane motif. Minor product **35** is analogous to the alkylidene formed in our earlier model studies,[9] except the material is now fully functionalized and properly chlorinated. A vicinal C17H/C18H coupling constant of 12.8 Hz implies the *trans* stereochemistry shown,[16] although we have yet to assign configuration at C16. Interestingly, the major products of the reaction appear to be C10 epimers of polycycle **36**. This unique structure is rationalized in terms of a rebound addition of the guanidine unit at N1 to N6 of an acyl iminium species generated transiently upon spirocycle formation (Scheme 8B), rather than the deprotonation of H_a that presumably affords **35**.[34] While we have yet to characterize **36** crystallographically, all spectroscopic measurements as well as mass spectra are consistent with the assignment. Note that the C17H/C18H *cis* ($J = 3.9$ Hz) stereochemistry proposed in **36** differs from **35**. Our initial argument that the hydrazide constraint in **24** would be required to establish this arrangement seems in error. That said, several reaction variables are ambiguous: the reacting alkylidene geometry, the reversibility of the spirocyclization, and the identity of the halogen transfer species. Nevertheless, upon chlorination we find crude mixtures contain alkylidene **35** having data consistent with C17/C18 *trans* stereochemistry, whereas isolated polycycles **36** display the corresponding substituents in a *cis* relation. A lack of coupling between C11H and C12H and a weak NOESY correlation between C11H and the C13 methylene protons imply C11/C12 *trans* stereochemistry in **36** and, to the extent the diazabicyclooctane motif can be assumed *cis* fused, the C16 C−N bond would be oriented β.

Another intriguing finding was made using $MgBr_2 \cdot Et_2O$ in place of $MgCl_2$ during the halogenation. In that case, we obtained only **38**, wherein C17 was substituted with bromine rather than chlorine.[35] The yield of product had nearly tripled, and the corresponding alkylidene **37** could not be detected in crude reaction mixtures. Like **36**, pentabromide **38** was isolated as a mixture of C10 epimers. The major epimer was treated with Et_3BHLi followed by anhydrous TiF_4 powder in toluene to afford a mixture of SEM-deprotected hemiaminal isomers.[36] We tentatively assign structure **39** to these materials.

The above results were encouraging. However, we were uncertain if comparable reactivity could be observed in the C_2-symmetric series, which is configured appropriately to reach revised palau'amine structure **1b**. Catalyzed hydrosilylation remained an effective method of reducing the dimer, in this case with C_2-**21** affording saturated isomers **40** (Scheme 9). However, unlike the synthesis of **34** from **33**, isomers **40** reacted chaotically with KHMDS, giving intractables, both with and without added Cy_2BOTf. This was a persistent difficulty, and considerable time passed before an alternative was found. Ultimately, treating a CH_3CN/DMF solution of **40** with excess proazaphosphatrane **42**[37] at ambient temperature provided doubly ring-opened, partially debrominated bis-alkylidene **43**. If care was taken to avoid decomposition during isolation, it was possible to obtain **43** in 40% yield, contaminated with only trace impurities. We know of no precedent for this remarkable process wherein two N−N σ bonds are cleaved and two heteroaryl carbon bromine bonds are reduced in a single operation.

(33) Attempts to assign olefin geometry in this system using $^3J_{CH}$ couplings were inconclusive. *Z* stereochemistry was thus inferred by analogy; see: Guella, G.; Mancini, I.; Zibrowius, H.; Pietra, F. *Helv. Chim. Acta* **1989**, *72*, 1444–1450.

(34) We have yet to observe products consistent with N5 trapping of the iminium species in B (Scheme 8). However, it is possible that **35** is a ring-opened product derivative of such a pathway.

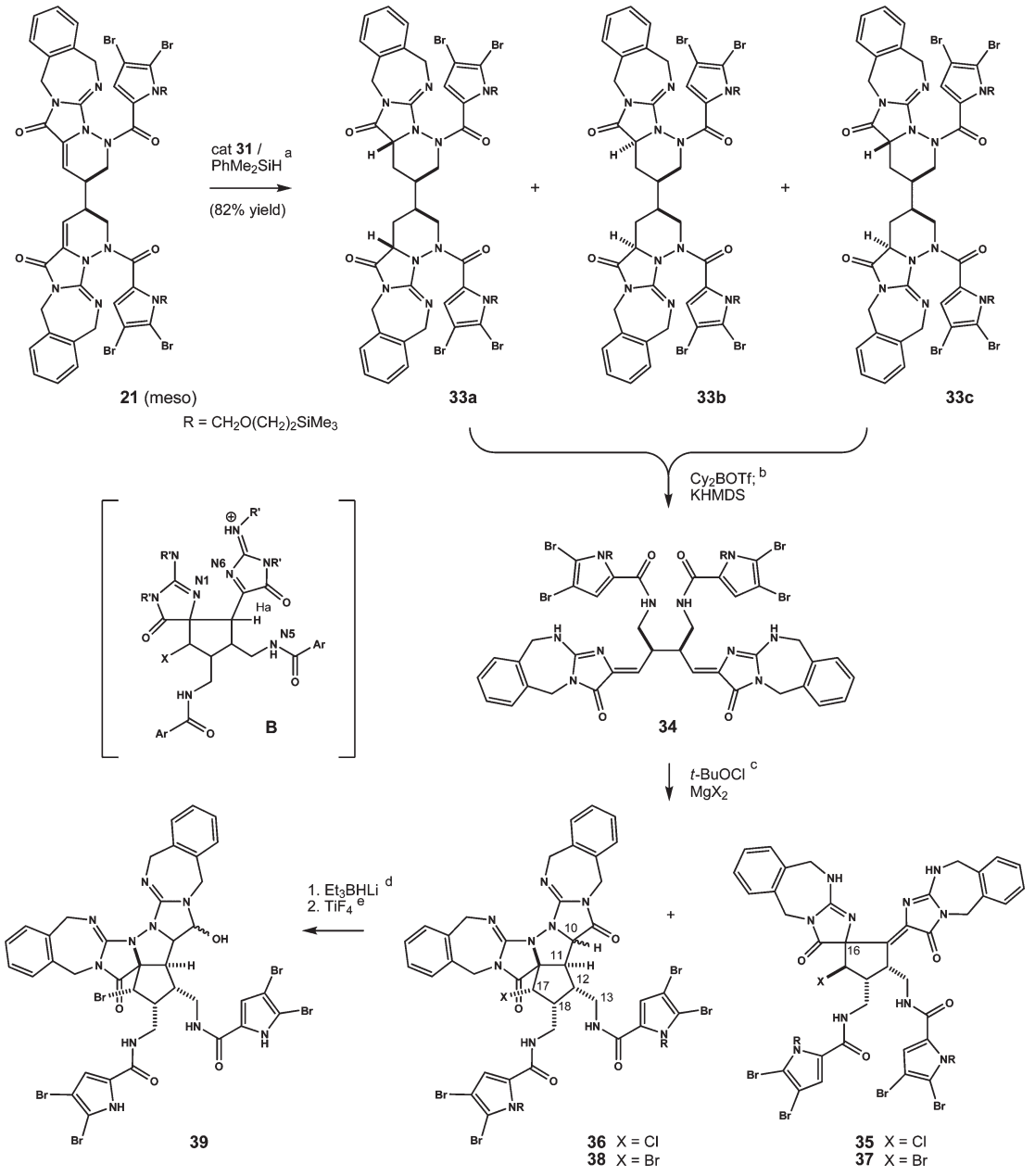
(35) The reaction of *t*-BuOCl with $MgBr_2$ to generate Br-Cl in situ is one rationale for this result.

(36) We are not aware of precedent for TiF_4-mediated SEM group removal. Conventional methods were ineffective in this case.

(37) Wroblewski, A. E.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 420–425.

(38) The reduction of **21** (C_2) to diastereomers **40** can also be accomplished using Zn dust in refluxing AcOH/THF. This provides **40** (40% yield) along with mono reduced material (20% yield, analogous to **27**) after 30 min in the presence of 4 equiv of Zn. Extended reaction times or a larger excess of Zn leads to partial debromination.

SCHEME 8[a]

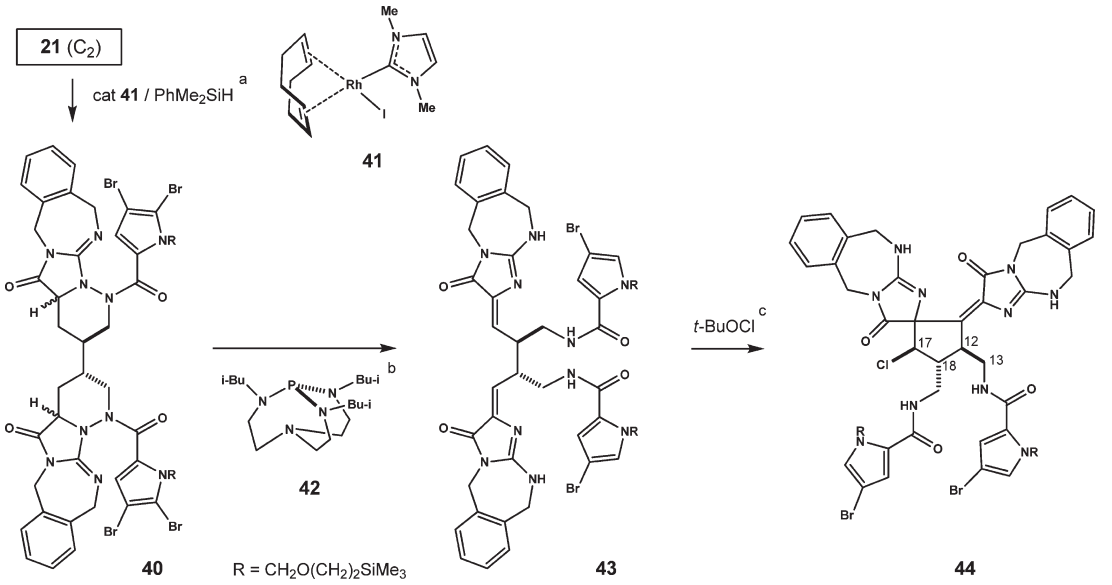


[a]Reaction conditions: (a) NH_4PF_6 pretreatment; 5 mol % of **31**, 5 mol % of 2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl, $PhMe_2SiH$ (2.1 equiv), MgI_2 (0.5 equiv), CH_2Cl_2, 55 °C, 18 h (**33a** + **33b**:**33c** = 4:1, 82%); (b) 3 equiv of Cy_2BOTf, 4.8 equiv of KHMDS THF, −78 °C to rt, 20 min (50%); (c) *t*-BuOCl (1.1 equiv), MgX_2 (1.5 equiv), THF/CH_2Cl_2, −78 °C, 2 h (when X = Cl: 26% of **36** + 8% of **35** + 30% of **34**; when X = Br: 70% of **38**, **37** not detected); (d) Et_3BHLi (5 equiv), toluene, −78 °C (70%); (e) TiF_4 (10 equiv), CH_2Cl_2, sealed vial, 80 °C, 30 min (80%). Structure **33b** has been characterized by X-ray crystallography.

Bis-alkylidene **43** is prone to decomposition, although when pure, the material could be dissolved in cold CH_2Cl_2 and treated with *t*-BuOCl to generate spirocyclic monoalkylidene **44**. In contrast to reactions in the *meso* series, added $MgCl_2$ or $MgBr_2$ was neither beneficial nor steered the outcome toward polycycles analogous to **36**. In fact, Lewis acidic additives were generally detrimental. Our best result employed *t*-BuOCl alone, affording **44** in 20−32% yield, with the mass balance being intractable, seemingly oligomeric materials.

This result validates our thesis, and despite low yields at present, we anticipate optimizations. Chloride **44** is the sole isolable product from the oxidation, which is the tenth linear step in our sequence. The C17H/C18H *trans* relation is supported by a vicinal coupling constant of 11.6 Hz.[16] The C18H/C12H *trans* relation is thought to be maintained during the oxidation and is consistent with ROESY correlations in **44** between C18H and the C13 methylene protons as well as between C12H and C17H. While the alkylidene geometry and relative configuration at C16 are not yet known, the former will likely be inconsequential and the

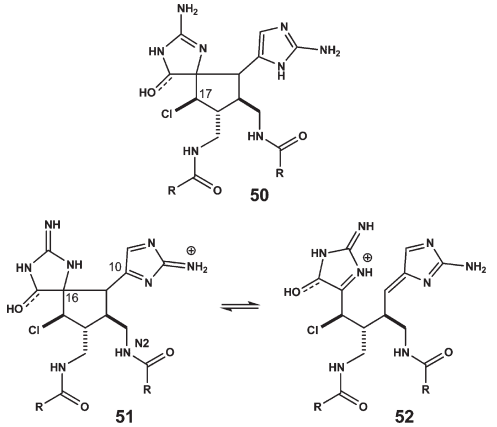
SCHEME 9[a]



[a]Reaction conditions: (a) NH_4PF_6 pretreatment; 15 mol % of **41**, 17 mol % of 2-(dicyclohexyiphosphino)-2-(*N*,*N*-dimethylamino)biphenyl, $PhMe_2SiH$ (2.1 equiv), LiI (1.1 equiv), CH_2C1_2, 55 °C, 72 h (82%) (ref 38); (b) 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phosophabicyclo[3.3.3]undecane (10 equiv), CH_3CN/DMF, rt, 14 h (40%); (c) *t*-BuOCl (1.2 equiv), CH_2Cl_2, −78 °C, 1 h (20−32%). One diastereomer of **40** has been characterized by X-ray crystallography (ref 17).

latter potentially adjustable (via equilibration) in the context of more complete intermediates.[39,40] Most importantly, confident that bis-alkylidenes of type **34**/**43** can be precursors to the halogenated core common to palau'amine and its relatives, we can now focus on tactical refinements needed for total syntheses. These include substrate modifications to (1) better manage stability and basicity of intermediates, (2) permit more ready unveiling of free guanidine functionality[41], (3) tunably dictate stereochemical outcomes, and (4) generate optically active end products. Studies along these lines are ongoing.

(39) In future iterations of the route (see ref 41), one path forward could entail transforming a structure of type **44** into an aminoimidazole of type **50**. Installation of the dipyrrolopyrazinone motif required to complete palau'amine would then parallel Büchi's phakellin synthesis (ref 40). Presuming that process would involve **51** as an intermediate, an equilibrium established with **52** (analogous to the species thought generated from **43** en route to **44**) prior to C10−N2 bond formation would render mute C16 stereochemistry in **44**. We look forward to exploring these issues in detail.



(40) Foley, L. H.; Büchi, G. *J. Am. Chem. Soc.* **1982**, *104*, 1776–1777.

(41) The 1,3-benzodiazepine ring system used to mask guanidine functions in this work was intended to facilitate oxidative spirocyclization, wherein substrates **34**/**43** might adopt compact globular forms in high dielectric solvents, juxtaposing the tethered alkylidenes. To date, we see no evidence for such behavior nor have we succeeded in degrading the benzodiazepine units to the corresponding free glycocyamidines in various intermediate settings. Alternatives are being pursued.

Experimental Section

Pyrrole Monomer 20. A mixture of **19** (34 g, 50 mmol), $HgCl_2$ (19 g, 67 mmol), and pyridine (12.1 mL, 150 mmol) in CH_3CN (250 mL) was heated at reflux for 3 h. A second portion of $HgCl_2$ (2.7 g, 13.4 mmol) was added and reflux continued for 1 h. Upon cooling the mixture to rt, a white solid was removed by filtration and the solvent was evaporated in vacuo. The reaction mixture was taken up in EtOAc, and the undissolved solids were removed by filtration. The organic layer was washed with 1 N NaOH, whereupon a white precipitate formed. The precipitate was filtered, and the NaOH wash/filtration sequence continued until no further solid formed (6−7×). The organic layer was then washed with water and brine and dried over $NaSO_4$. Concentration in vacuo and purification by silica gel chromatography (1:3 EtOAc/hexanes) afforded **20** as a white foam (15.0 g). Mixed fractions were purified on a second silica gel column (1:9 EtOAc/CH_2Cl_2) to provide a further 5.0 g of **20** (total yield = 70%): R_f = 0.7 (1:9 CH_3CN/$CHCl_3$); IR (film) 2951, 1741, 1635, 1402, 1093, 859, 758, 793 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 7.38−7.28 (m, 4H), 6.81 (s, 1H), 5.82 (t, J = 4.7 Hz, 1H), 5.60 (s, 2H), 4.89 (s, 2H), 4.66 (s, 2H), 3.92−3.75 (m, 2H), 3.57 (t, J = 12 Hz, 2H), 2.33 (dd, J = 5.3, 10.4 Hz, 2H), 0.88 (t, J = 12 Hz, 2H), 0.0 (s, 9H); ^{13}C NMR (100 MHz, CD_3CN): δ 163.8, 159.3, 141.6, 141.4, 134.9, 129.5, 129.2, 129.1, 129.0, 126.3, 118.7, 118.0, 112.6, 104.2, 100.2, 76.1, 66.7, 49.5, 45.7, 43.6, 23.5, 18.2, −1.3; HRMS (ESI-TOF) calcd for $C_{25}H_{30}Br_2N_5O_3Si$ $(M+H)^+$ 634.0479, found 634.0483.

***Meso* and C_2 Symmetric Dimers 21.** Monomer **20** (311 mg, 0.49 mmol) and solid $(i\text{-PrCp})_2TiCl_2$ (190 mg, 0.57 mmol) were dissolved in anhydrous THF (2.5 mL). The brandy-colored solution was degassed via consecutive freeze−pump−thaw cycles (3×) and cooled to −78 °C. KHMDS (1.08 mL, 0.5 M in toluene) was added dropwise, and the resultant dark green slurry was stirred at −78 °C for 1.5 h. A fine suspension of $Cu(OTf)_2$ (260 mg, 0.74 mmol) in dry, degassed THF was added

over 15 min, and the dark red/brown slurry stirred at −78 °C for 3 h and then at rt for 1.5 h. The reaction was treated with pH 8.0 aq EDTA (5 mL, 0.35 M), and the volatiles were removed in vacuo. The residue was diluted in EtOAc and washed with additional pH 8.0 EDTA solution (until blue color no longer observed), H_2O, and brine. The organics were dried over Na_2SO_4, filtered, and concentrated. Purification by column chromatography on silica gel (1% $CH_3CN/CHCl_3$) afforded *meso*-**21** (150 mg, 49%) and C_2-**21** (45 mg, 15%). *meso*-**21**: light yellow solid; R_f = 0.35 (10% $CH_3CN/CHCl_3$); IR (film) 1745, 1745, 1698, 1447, 1396, 1093, 934, 836 cm^{-1}; ^1H NMR (400 MHz, CD_3CN, 70 °C) δ 7.40−7.20 (m, 8H), 6.71 (s, 2H), 5.66−5.48 (m, 6H), 4.95 (s, 4H), 4.62 (s, 4H), 3.77 (bs, 4H), 3.57 (t, J = 8.0 Hz, 4H), 2.49 (s, 2H), 0.86 (t, J = 8.0 Hz, 4H), 0.01 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$, 55 °C) δ 163.0, 158.4, 140.7, 140.2, 133.6, 130.3, 129.3, 128.8, 128.7, 128.5, 125.3, 118.0, 112.4, 104.0, 100.2, 75.6, 66.5, 49.6, 45.6, 43.6, 36.5, 18.2, −1.2; HRMS (ESI-TOF) calcd for $C_{50}H_{57}Br_4N_{10}O_6Si_2$ $(M+H)^+$ 1265.0729, found 1265.0730. Crystals of *meso*-**21** suitable for X-ray diffraction were grown from MeOH (slow evaporation). Details of the crystallographic analysis are provided in a separate CIF file (Supporting Information). C_2-**21**: light yellow solid; R_f = 0.2 (10% $CH_3CN/CHCl_3$); IR (film) 1745, 1698, 1448, 1397, 1093, 934, 836 cm^{-1}; ^1H NMR (400 MHz, CD_3CN, 70 °C) δ 7.40−7.20 (m, 8H), 6.72 (s, 2H), 5.72 (s, 2H), 5.51(s, 4H), 4.95 (s, 4H), 4.61(S, 4H), 3.87 (bs, 4H), 3.58 (t, J = 8 Hz, 4H), 2.49 (s, 2H), 0.86 (t, J = 8 Hz, 4H), 0.01 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$, 55 °C) δ 163.0, 158.5, 140.7, 140.2, 133.6, 130.2, 129.3, 128.8, 128.5, 125.0, 118.1, 112.5, 103.7, 100.2, 75.6, 66.6, 49.6, 46.4, 43.6, 36.7, 18.2, −1.2; HRMS (ESI-TOF) calcd for $C_{50}H_{57}Br_4N_{10}O_6Si_2$ $(M+H)^+$ 1265.0729, found 1265.0707.

Catalyzed Reduction of Dimer C_2-21 to 40. A 25 mL flame-dried flask was charged with C_2-**21** (2.0 g, 1.58 mmol), NH_4PF_6 (770 mg, 4.72 mmol), LiI (233 mg, 1.74 mmol), and THF (7.9 mL), and the mixture was stirred at rt for 10 min. The solvent was removed in vacuo. A separate 25-mL flame-dried flask was charged with 100 mg of cyclooctadiene *N*,*N*-dimethylimidazolium rhodium(I) iodide **41** (0.24 mmol, 15 mol %), 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (102 mg, 0.26 mmol, 17 mol %), and CH_2Cl_2 (7.9 mL). $PhMe_2SiH$ (644 mg, 4.72 mmol) was added, and the resulting solution was stirred at rt for 5 min. This catalyst solution was added to the flask containing **21**, and the resulting suspension was heated at 50 °C for 72 h. Upon cooling to rt, the reaction mixture was quenched with saturated $NaHCO_3$ and diluted with CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification via column chromatography on silica gel (gradient from 5% → 50% $CH_3CN/CHCl_3$) gave 928 mg of **40a** that was roughly 60% pure. This was followed by **40b** (840 mg, 42%). Pure **40a** was obtained by triturating with CH_3CN (yield ∼30%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.25 (m, 8H), 6.82 (s, 2H), 5.81 (d, J = 10.5 Hz, 2H), 5.36 (d, J = 10.5 Hz, 2H), 4.90 (d, J = 19.2 Hz, 2H), 4.87 (d, J = 19.2 Hz, 2H), 4.73 (d, J = 19.2 Hz, 2H), 4.70 (d, J = 19.2 Hz, 2H), 4.45 (d, J = 12.8 Hz, 2H), 3.73−3.70 (m, 2H), 3.62 (dd, J = 11.6, 4.5 Hz, 2H), 3.45 (ddd, J = 9.0, 6.9, 1.9 Hz, 4H), 2.49 (dd, J = 12.7, 11.3 Hz, 2H), 2.11−2.08 (m, 2H), 1.59−1.54 (m, 2H), 1.20−1.07 (m, 2H), 0.89−0.74 (m, 2H), −0.06 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 163.7, 145.1, 140.1, 133.0, 129.4, 128.6, 128.5, 128.4, 128.3, 125.2, 117.3, 111.0, 99.4, 75.1, 66.1, 56.2, 49.2, 43.3, 34.9, 29.9, 17.9, −1.4; MS for $C_{50}H_{61}Br_4N_{10}O_6Si_2$ (ESI+) m/z (relative intensity) 1273 (M^+ + 1, 100). **40b**: ^1H NMR (500 MHz, CD_3CN, 70 °C) δ 7.37−7.27 (m, 7H), 7.24−7.20 (m, 1H), 6.77 (s, 1H), 6.75 (s, 1H), 5.61 (d, J = 10.7 Hz, 1H), 5.59 (s, 2H), 5.54 (d, J = 10.7 Hz, 1H), 4.95−4.87 (m, 4H), 4.75 (d, J = 14.5 Hz, 1H), 4.70 (d, J = 14.4 Hz, 1H), 4.62 (d, J = 14.5 Hz, 1H), 4.60 (d, J = 14.5 Hz, 1H), 4.56−4.43 (m, 1H), 4.12 (t, J = 6.1 Hz, 1H), 4.01 (dd, J = 12.9, 7.3 Hz, 1H), 3.81 (dd, J = 11.6, 4.9 Hz, 1H), 3.59 (t, J = 8.1 Hz, 2H), 3.57 (t, J = 8.1 Hz, 2H), 3.26 (dd, J = 12.9, 5.3 Hz, 1H), 2.33 (t, J = 12.2 Hz, 1H), 2.18−2.16 (m, 1H), 1.91−1.86 (m, 1H), 1.78−1.69 (m, 2H), 1.28−1.21 (m, 1H), 1.04 (q, J = 12.2 Hz, 1H), 0.97−0.82 (m, 4H), 0.01 (s, 9H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, CD_3CN) δ 172.1, 171.3, 164.9, 164.6, 149.1, 148.0, 135.8, 135.7, 130.8, 130.7, 130.3, 130.2, 130.0, 129.9, 128.7, 128.5, 118.3, 111.8, 111.5, 100.8, 100.7, 77.5, 67.9, 58.0, 50.5, 50.3, 45.1, 44.9, 34.8, 34.4, 31.9, 27.9, 19.6, 19.5, −0.4; HRMS (ESI-TOF) calcd for $C_{50}H_{61}Br_4N_{10}O_6Si_2$ $(M+H)^+$ 1269.1042, found 1269.1038.

Symmetric Bis-alkylidene 43. A flame-dried 5 mL flask was charged with **40a** or **40b** (100 mg, 78.6 μmol), DMF (830 μL), and CH_3CN (330 μL) at rt. 2,8,9-Triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.0]undecane (269 mg, 786 μmol) was added, and the resulting mixture was stirred at rt for 22 h. The dark reddish purple mixture was diluted with EtOAc and washed with saturated aqueous NH_4Cl, water, saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel slurry packed (1% $Et_3N-CH_2Cl_2$) and eluted (2% $MeOH-CH_2Cl_2$) to give the desired product in yields ranging from 30 to 50%. Pure **43** was obtained using HPLC (5 μm C-18 column, 250 × 10 mm, 85% CH_3CN/H_2O, 8 mL/min, UV detection at 254 nm; t_R = 6.0 min): ^1H NMR (500 MHz, CD_3CN) δ 7.48 (bs, 2H), 7.42−7.31 (m, 8H), 6.97 (d, J = 1.8 Hz, 2H), 6.63 (d, J = 1.8 Hz, 2H), 5.60 (d, J = 10.2 Hz, 2H), 5.51 (d, J = 9.2 Hz, 2H), 5.42 (d, J = 10.2 Hz, 2H), 4.91 (d, J = 18.2 Hz, 2H), 4.88 (d, J = 18.2 Hz, 2H), 4.62 (d, J = 14.9 Hz, 2H), 4.52 (d, J = 14.8 Hz, 2H), 3.46−3.38 (m, 6H), 3.18−3.06 (m, 4H), 0.79−0.70 (m, 4H), −0.12 (s, 18H); ^{13}C NMR (100 MHz, CD_3CN) δ 167.5, 161.6, 140.3, 136.5, 130.3, 130.0, 129.7, 128.7, 127.4, 116.2, 115.9, 96.4, 77.7, 67.1, 46.1, 44.2, 41.7, 30.8, 18.7, 18.6, 0.0; MS calcd for $C_{50}H_{63}Br_2N_{10}O_6Si_2$ (ESI+) m/z (relative intensity) 1115.30, found 1115.00.

Spirocyclic Alkylidene Chloride 44. Symmetric bis-alkylidene **43** (18 mg, 16.1 μmol) was dissolved in CH_2Cl_2 (150 μL), and the resulting solution was cooled to −78 °C. A stock solution of *tert*-butyl hypochlorite (20 μL) in CH_2Cl_2 (500 μL) was prepared fresh at rt prior to use. A 50 μL portion of this stock solution was added to the solution of **43**, and stirring was continued at −78 °C for 10 min. After being warmed to rt, the mixture was diluted with CH_2Cl_2 and washed with saturated aq $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by preparative thin-layer chromatography (9% $MeOH/CH_2Cl_2$) gave 6.4 mg (36%) of **44**. Pure **44** was obtained after HPLC: analytical (5 μm C-18 column, 250 × 4.6 mm, 85% CH_3CN/H_2O, 1 mL/min, UV detection at 254 nm, t_R = 13.3 min); preparative (5 μm C-18 column, 250 × 10 mm, 85% CH_3CN/H_2O, 8 mL/min, UV detection at 254 nm, t_R = 7.5 min); ^1H NMR (500 MHz, CD_3CN) δ 8.15 (s, 1H), 7.48−7.45 (m, 1H), 7.42−7.36 (m, 2H), 7.35−7.26 (m, 6H), 7.02 (d, J = 1.9 Hz, 1H), 7.00 (d, J = 1.9 Hz, 1H), 6.83 (d, J = 1.7 Hz, 1H), 6.75 (d, J = 1.9 Hz, 1H), 5.61 (d, J = 10.3 Hz, 1H), 5.59 (d, J = 10.4 Hz, 1H), 5.58 (d, J = 10.3 Hz, 1H), 5.56 (d, J = 10.3 Hz, 1H), 4.92 (s, 2H), 4.73 (s, 2H), 4.56 (d, J = 14.8 Hz, 1H), 4.49 (d, J = 15.0 Hz, 1H), 4.49 (d, J = 15.0 Hz, 1H), 4.38 (d, J = 15.0 Hz, 2H), 4.01 (d, J = 11.6 Hz, 1H), 3.77 (ddd, J = 13.1, 4.3, 4.3 Hz, 1H), 3.65 (ddd, J = 14.3, 6.0, 4.3 Hz, 1H), 3.49−3.38 (m, 4H), 3.46 (t, J = 2.0 Hz, 2H), 3.13 (ddd, J = 8.8, 4.1, 4.1 Hz, 1H), 2.32−2.25 (m, 1H), 0.79 (t, J = 2.0 Hz, 2H), 0.77−0.71 (m, 2H), −0.10 (s, 9H), −0.14 (s, 9H); ^{13}C NMR (100 MHz, CD_3CN): δ 178.9, 166.5, 162.5, 162.4, 158.9, 158.7, 140.3, 139.8, 138.5, 136.6, 136.4, 130.8, 130.3, 130.2, 130.1, 129.9, 129.8, 129.7, 129.3, 129.0, 128.3, 127.8, 127.3, 116.8, 116.5, 96.4, 96.3, 78.0, 77.6, 76.6, 69.7, 67.2, 67.0, 47.8, 46.0, 45.7, 45.2, 45.0, 44.1, 42.9, 40.2, 18.6, −1.0; HRMS (ESI-TOF) calcd for $C_{50}H_{63}Br_2ClN_{10}O_6Si_2$ $(M+H)^+$ 1147.2442, found 1147.2432.

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Supporting Information Available: Experimental procedures, characterization data for all new compounds, and crystallographic data for intermediates **12**, **13**, **21**-***meso***, **29**, **33b**, and **40a**. This material is available free of charge via the Internet at http://pubs.acs.org.