Published in final edited form as:

J Org Chem. 2009 August 21; 74(16): 5909–5919. doi:10.1021/jo900755r.

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

Qingyi Li^{†,§}, Paul Hurley^{†,‡,#}, Hui Ding[‡], Andrew G. Roberts[‡], Radha Akella[†], and Patrick G. Harran[‡]

[‡]Department of Chemistry and Biochemistry, University of California Los Angeles, 607 Charles E. Young Drive East, Los Angeles, CA 90095-1569

[†]Department of Biochemistry, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd, Dallas, Texas 75390-9038

Abstract

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) 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^{2a} - perhaps wherein genes encoding enzymatic machinery manipulating intermediates have transferred and evolved across producing species. An alternate view stems from Al-Mourabit's recent insightful work on autooxidative 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 anti-fungal constituent of *S. aurantium*.¹ The substance was also reported to possess anti-microbial activity and to inhibit stimulated human T-cell proliferation *in vitro*, while being relatively innocuous to resting lymphocytes.

harran@chem.ucla.edu .

[§]Current address: Cubist Pharmaceuticals, Inc. 65 Hayden Avenue, Lexington, MA 02421.

[#]Current address: Gilead Alberta ULC, 1021 Hayter Road, Edmonton, AB, T6S 1A1, Canada.

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 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 very recently reported the first synthesis of axinellamines and massadines - truly seminal achievements.^{8a,b} 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 $(\text{CO}_2\text{Et})_2$ 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 carboxylate¹¹ that was subsequently allylated and saponified to afford **8**. When carboxylic acid **8** was condensed with *o*-xylyl diamine-derived methylisothiurea **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*-amino glycoamidine **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 $\text{FeCl}_2(\text{DMF})_3\text{FeCl}_4$ ¹⁵ generated dimeric products efficiently. With the original assignment of palau'amine stereochemistry^{1,16} (namely, **1a**) 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 $\text{FeCl}_2(\text{DMF})_3\text{FeCl}_4$ 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, $\text{FeCl}_2(\text{DMF})_3\text{FeCl}_4$ 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 $[i\text{-PrCp}]_2\text{TiCl}_2$ 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 Schmittl'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 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 $[i\text{-PrCp}]_2\text{TiCl}_2$ prior to KHMDS, subsequent oxidation with $\text{Cu}(\text{OTf})_2$ afforded dimers **21** (3.3:1 *meso*: C_2) in respectable yield (Scheme 5). Notably, changing the oxidant to $\text{FeCl}_2(\text{DMF})_3\text{FeCl}_4$ 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 sigma 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 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 glycoamidine units would react preferentially to give products having a *trans* relationship between ring substituents at 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 pre-treated with 2 equiv. 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 pre-treatment 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 diazabicyclic in **28** was identical to that targeted in **25**, just lacking halogen on the methano bridge. X-ray diffraction analysis of crystals grown from samples of SEM-deprotected **28** showed 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** towards **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 an equivalent 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 mono-reduced dimer was evidently not a method to access **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 re-interpretation of spectroscopic data collected on palau'amine itself, suggested the molecule was epimeric at carbons 12 and 17, wherein **1b** (Figure 1) 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 (Fig 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 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 non-symmetric material **33c**. This was of no preparative consequence. After careful experimentation, we found the isomeric mixture could be treated with excess Cy₂BOTf, 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 MgCl₂, cooled to -78 °C and treated with freshly prepared *t*-BuOCl, we obtained three chlorinated products - all of which data suggests 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 beta.

Another intriguing finding was made using MgBr₂·Et₂O in place of MgCl₂ 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 Et₃BHLi followed by anhydrous TiF₄ 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 C₂-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 C₂-**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 Cy₂BOTf. This was a persistent difficulty and considerable time passed before an alternative was found. Ultimately, treating a CH₃CN/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

sigma bonds are cleaved and two heteroaryl carbon bromine bonds are reduced in a single operation.

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 mono-alkylidene **44**. In contrast to reactions in the *meso* series, added MgCl_2 or MgBr_2 was neither beneficial nor steered the outcome towards 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 10th 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 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 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 functionality⁴¹ 3) tunably dictate stereochemical outcomes, and 4) generate optically-active end products. Studies along these lines are ongoing.

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 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 1N NaOH whereupon a white precipitate formed. The precipitate was filtered and the NaOH wash / filtration sequence continued until no further solid formed (6-7 $\times$). 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 $\text{C}_{25}\text{H}_{30}\text{Br}_2\text{N}_5\text{O}_3\text{Si}$ ($\text{M}+\text{H}$)⁺: 634.0479; found: 634.0483.

Meso and C₂ symmetric dimers 21

Monomer **20** (311 mg, 0.49 mmol) and solid $[\text{i-PrCp}]_2\text{TiCl}_2$ (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 $\times$) 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 $\text{Cu}(\text{OTf})_2$ (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 3h 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, washed with additional pH 8.0 EDTA solution (until blue color no longer observed), H₂O and brine. The organics were dried over Na₂SO₄, filtered and concentrated. Purification by column chromatography on silica gel (1% CH₃CN/CHCl₃) afforded **21 meso** (150 mg, 49%) and **21 C₂** (45 mg, 15%). **21 meso**: light yellow solid; *R_f* = 0.35 (10% CH₃CN/CHCl₃); IR (film): 1745, 1745, 1698, 1447, 1396, 1093, 934, 836 cm⁻¹; ¹H NMR (400 MHz, CD₃CN, 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); ¹³C NMR (75 MHz, CDCl₃, 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 C₅₀H₅₇Br₄N₁₀O₆Si₂ (M+H)⁺ 1265.0729, found 1265.0730. Crystals of **21 meso** suitable for X-ray diffraction were grown from MeOH (slow evaporation). Details of the crystallographic analysis are provided in a separate CIF file. **21 C₂**: light yellow solid; *R_f* = 0.2 (10% CH₃CN/CHCl₃); IR (film): 1745, 1698, 1448, 1397, 1093, 934, 836 cm⁻¹; ¹H NMR (400 MHz, CD₃CN, 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); ¹³C NMR (75 MHz, CDCl₃, 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 C₅₀H₅₇Br₄N₁₀O₆Si₂ (M+H)⁺: 1265.0729; found: 1265.0707.

Catalyzed reduction of dimer **21-C₂** to **40**

A 25 mL flame-dried flask was charged with **21 C₂** (2.0 g, 1.58 mmol), NH₄PF₆ (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 CH₂Cl₂ (7.9 mL). PhMe₂SiH (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 NaHCO₃ and diluted with CH₂Cl₂. The aqueous layer was separated and extracted with CH₂Cl₂. The combined organics were dried over MgSO₄, filtered and concentrated *in vacuo*. Purification via column chromatography on silica gel (gradient from 5%→50% CH₃CN/CHCl₃) 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 CH₃CN (yield ~30%). ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 C₅₀H₆₁Br₄N₁₀O₆Si₂ (ESI+) *m/z* (relative intensity): 1273 (M⁺+1, 100). **40b**: ¹H NMR (500 MHz, CD₃CN @ 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). ¹³C NMR (100 MHz, CD₃CN): 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 μ mol), DMF (830 μ L) and CH_3CN (330 μ L) at rt. 2,8,9-Triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.0]undecane (269 mg, 786 μ mol) 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 30-50%. Pure **43** was obtained using HPLC (5 μ m C-18 column, 250 $\times$ 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). ¹³C 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 μ mol) was dissolved in CH_2Cl_2 (150 μ L) and the resulting solution was cooled to -78 °C. A stock solution of *tert*-butylhypochlorite (20 μ L) in CH_2Cl_2 (500 μ L) was prepared fresh at rt prior to use. 50 μ L of this stock solution was added to the solution of **43** and stirring was continued at -78 °C for 10 min. After warming 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 μ m C-18 column, 250 $\times$ 4.6 mm, 85 % CH_3CN / H_2O , 1 mL/min, UV detection at 254 nm, T_R = 13.3 min); preparative (5 μ m C-18 column, 250 $\times$ 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). ¹³C 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding was provided by the NIH (RO1-GM60591), the Robert A. Welch Foundation, the Chilton Family Endowment, the Donald J. & Jane M. Cram Endowment, and unrestricted research awards from Merck and Pfizer. A large portion of this work was carried out at the University of Texas Southwestern (UTSW) Medical Center where Q. Li was a Robert A. Welch Foundation Graduate Fellow. We are grateful to Drs. Ranny Mathew Thomas, Jian Wang and Christopher Lindsey for valuable experimental assistance.

REFERENCES

- (1). a) Kinnel RB, Gehrken H-P, Scheuer PJ. *J. Am. Chem. Soc* 1993;115:3376–3377. b) Kinnel RB, Gehrken H-P, Swali R, Skoropowski G, Scheuer PJ. *J. Org. Chem* 1998;63:3281–3286.
- (2). a) Al-Mourabit, P. Potier *Eur. J. Org. Chem* 2001:237–243. b) Baran PS, O'Malley DP, Zografos AL. *Angew. Chem. Int. Ed* 2004;43:2674–2677. c) Grube A, Immel S, Baran PS, Köck M. *Angew. Chem. Int. Ed* 2007;46:6721–6724.
- (3). Wright AE, Chiles SA, Cross SS. *J. Nat. Prod* 1991;54:1684–1686.
- (4). a) Garcia EE, Benjamin LE, Fryer RI. *J. Chem. Soc., Chem. Comm* 1973:78–79. b) Gautschi JT, Whitman S, Holman TR, Crews P. *J. Nat. Prd* 2004;67:1256–1261.
- (5). a) Ravert N, Al-Mourabit A. *J. Am. Chem. Soc* 2004;126:10252–10253. [PubMed: 15315431] b) Vergne C, Boury-Esnault N, Perez T, Martin M-T, Adeline M-T, Dau ETH, Al-Mourabit A. *Org. Lett* 2006;8:2421–2424. [PubMed: 16706541] c) Vergne C, Appenzeller J, Ratinaud C, Martin M-T, Debitus C, Zaparucha A, Al-Mourabit A. *Org. Lett* 2008;10:493–496. [PubMed: 18171071]
- (6). For reviews see: a) Köck M, Grube A, Seiple IB, Baran PS. *Angew. Chem. Int. Ed* 2007;46:6586–6594. b) Jacquot DEN, Lindel T. *Curr. Org. Chem* 2005;9:1551–1565. For recent contributions see: c) Namba K, Kaihara Y, Imagawa I, Tanino K, Williams RM, Nishizawa M. *Chem.—Eur. J.* 2009 Early View, DOI: 10.1002/chem.200900622. d) Hudon J, Cernak TA, Ashenhurst JA, Gleason JL. *Angew. Chem. Int. Ed* 2008;47:8885–8888. e) Cernak TA, Gleason JL. *J. Org. Chem* 2008;73:102–110. [PubMed: 18067312] f) Bultman MS, Ma J, Gin DY. *Angew. Chem. Int. Ed* 2008;47:6821–6824. g) Zancanella MA, Romo D. *Org. Lett* 2008;10:3685–3688. [PubMed: 18693745] h) Wang S, Romo D. *Angew. Chem. Int. Ed* 2008;47:1284–1286. i) Sivappa R, Hernandez NM, He Y, Lovely CJ. *Org. Lett* 2007;9:3861–3864. [PubMed: 17803309] j) Spoering, RM. Ph.D Thesis. Harvard University; 2005. Studies Toward a Synthesis of Palau'amine.
- (7). Lanman BA, Overman LE, Paulini R, White NS. *J. Am. Chem. Soc* 2007;129:12896–12900. and refs therein. [PubMed: 17902668]
- (8). a) O'Malley DP, Yamaguchi J, Young IS, Seiple IB, Baran PS. *Angew. Chem. Int. Ed* 2008;47:3581–3583. b) Su S, Seiple IB, Young IS, Baran PS. *J. Am. Chem. Soc* 2008;130:16490–16491. [PubMed: 19049446]
- (9). Garrido-Hernandez H, Nakadai M, Vimolratana M, Li Q, Doundoulakis T, Harran PG. *Angew. Chem. Int. Ed* 2005;117:765–769.
- (10). Öhler E, Schmidt U. *Chem. Ber* 1975:2907–2916.
- (11). Broger EM, Cramer Y, Imfeld M, Montavon F, Widmer R. *Eur. Pat. Appl.* 1993 EP 570764.
- (12). a) Kawahara S, Uchimar T. *Z. Naturforsch., B: Chem Sci* 2000;55:985–987. b) Elslager EF, Worth DF, Haley NF, Perricone SC. *J. Heterocycl. Chem* 1968;5:609–612.
- (13). a) Kauffmann T, Neissner G, Köppelmann BE, Legler J, Schönfelder M. *Angew. Chem. Intl. 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 MA. *J. Org. Chem* 1988;53:3745–3752. d) Porter NA, Su Q, Harp JJ, Rosenstein IJ, MaPhail AT. *Tetrahedron Lett* 1993;34:4457–4460. e) Schmitt M. *Top. Curr. Chem* 1994:183–230. f) Richter JM, Whitefield BW, Maimone TJ, Lin DW, Castroviejo MP, Baran PS. *J. Am. Chem. Soc* 2007;129:12857–12869. [PubMed: 17900115]
- (14). The yield of dimeric products in non-deoxygenated solvents is lowered due to competing formation of angularly hydroxylated monomer **45**. **45** also forms (75% yield) when **11** is treated with KHMDS alone (1.1 equiv, -78 °C, 0.2M, 1h) in non-deoxygenated THF. **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 RWM, Matsunaga S. *Tetrahedron Lett* 2007;48:2127–2129. b) Buchanan MS, Carroll AR, Addepalli R, Avery VM, Hooper JNA, Quinn RJ. *J. Org. Chem* 2007;72:2309–2317. [PubMed: 17315930] 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.
- (17). A single diastereomer of **12**, the *dl* form of **13**, **21** *meso*, polycycle **29**, and reduction products **33b** have been characterized by X-ray crystallography. See supporting information for details.
- (18). *Meso* and racemic C_2 forms **14a/14b** are inseparable by silica gel chromatography. Ratios are determined by ^1H NMR and HPLC analyses (*Chiralcel-OD-H*, isocratic: 80% i-PrOH/hexanes).
- (19). $T^{1/2}$ for the conversion **13** $\rightarrow$ **12** in toluene solution at 85 °C is 56 minutes ($E_a \sim 27$ 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 FE, Harran PG. *J. Org. Chem* 1993;58:2768–2773.
- (22). A 0.1M THF solution of **13** is unchanged at room temperature after 2 hr in the presence of 0.6 equiv $\text{FeCl}_2(\text{DMF})_3\text{FeCl}_4$.
- (23). This statement reflects a corollary to the Hammond postulate. However, available data does 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 $\text{FeCl}_2(\text{DMF})_3\text{FeCl}_4$ - wherein significant amounts of α,γ -regioisomeric dimers are consistently observed (Schemes 2 & 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**.

11 ·HPF₆

TiF₄, toluene
 100 °C; aq Na₂CO₃

(27). Katz JD, Overman LE. Tetrahedron 2004;60:9559–9468.

(28). The use of sub-stoichiometric amounts of HgCl₂ in the reaction leads to isolation of angular thioether **46**. This material can be converted independently to **20** by re-exposure to HgCl₂ / pyr (CH₃CN, 70 °C).

- (29). Ojima I, Kogure T, Nagai Y. *Tetrahedron Lett* 1972;5035.
- (30). Voutchkova AM, Appelhans LN, Chianese AR, Crabtree RH. *J. Am. Chem. Soc* 2005;127:17624–17625. [PubMed: 16351090]
- (31). Anderson KW, Buchwald SL. *Angew. Chem. Int. Ed* 2005;44:6173–6177.
- (32). Blanchette MA, Choy W, Davis JT, Essinfeld AP, Masamune S, Roush WR, Sakai T. *Tetrahedron Lett* 1984;25:2183–2186.
- (33). Attempts to assign olefin geometry in this system using $^3J_{\text{CH}}$ 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 **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 AE, Verkade JG. *J. Org. Chem* 2002;67:420–425. [PubMed: 11798312]
- (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 Zn. Extended reaction times or a larger excess of Zn leads to partial debromination.
- (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 LH, 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 glycohydrazines in various intermediate settings. Alternatives are being pursued.

Scheme 1.

Reaction conditions: a) 1 equiv NH₂NH₂, 10 equiv AcOH, MeOH / H₂O, rt to 62 °C (>95%). b) 1 equiv KHMDS; 1.2 equiv allyl bromide, THF, -35 °C (90%). c) 1.5 equiv LiOH, 2:1:1 THF / MeOH / H₂O; aq citric acid (>95%). d) 1.1 equiv **9**, 1 equiv TBTU, 3 equiv (*i*-Pr)₂NEt, DMF, then concentrate *in vacuo* at 70 °C (72%). TBTU = 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate

Scheme 2.

Reaction conditions: a) 1.05 equiv KHMDS, degassed THF, -78 °C, 30 min; add 1.1 equiv oxidant and stir for 1 h at -78 °C. b) 0.02M **13** in degassed toluene, 95 °C, 1 h (81%). c) *hν* (Rayonet - 254 nm bulb set), 0.01 M in deoxygenated pH, 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* and racemic *C*₂ forms.

Scheme 3.

Reaction conditions: a) KHMDS (1.1 equiv), deoxygenated THF, -78 °C, 30 min; then [R-Cp]₂TiCl₂ (1.15 equiv), -78 °C, 3h; then Cu(OTf)₂ (1.6 equiv), 3.5h, -78 °C. b) 20% yield of **12** and 10% recovered **11** also isolated in this experiment.

Scheme 4.

Reaction conditions: a) 0.95 equiv **17**, pyr, CH₃CN, rt (94%). b) LiOH, 1:1 THF / H₂O, 0 °C (95% - recrystallized). c) 1.05 equiv **9**·HI, 1.1 eq TBTU, 3 equiv (*i*-Pr)₂NEt, DMF, rt (>95%). d) 1.5 equiv HgCl₂, 3 equiv pyr, CH₃CN, reflux, 3h (70%).

entry	oxidant	21 (meso:C ₂)	combined yield (%)
1	FeCl ₂ (DMF) ₃ ·FeCl ₄	1 : 3	62 ^b
2	Cu(OTf) ₂	3.3: 1	64

Scheme 5.

Reaction conditions: a) [*i*-PrCp]₂TiCl₂ (1.15 equiv), deoxygenated THF, 0 °C to -78 °C, 30 min; then KHMDS (1.1 equiv), -78 °C, 1.5h; then Cu(OTf)₂ (1.5 equiv) or FeCl₂(DMF)₃FeCl₄ (1 equiv), 3h, -78 °C to RT, 1.5h. 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).

Scheme 6.

A) Initial strategy to parley dimers **21** into palau'amine intermediates with control of relative stereochemistry. B) Reaction condition: a) NH₄PF₆ pre-treatment; 20 mol% (Ph₃P)₃RhCl, PhMe₂SiH (1.1 equiv), CH₂Cl₂, 45 °C, 24h b) NH₄PF₆ pre-treatment; 5 mol% **31**, 5 mol% 2-(dicyclohexylphosphino)-2'-(*N,N*-dimethylamino)biphenyl, PhMe₂SiH (1.1 equiv), MgI₂ (0.8 equiv), CH₂Cl₂, 45 °C, 18h (60% **27** + 11% **28**). c) same as (b) except NH₄PF₆ treatment omitted and MgBr₂·Et₂O (1.5 equiv) used in place of MgI₂ (45% **28** + 30% **27**). d) KHMDS (2.1 equiv), THF, -78 °C to RT, 1h, 85%. e) BF₃·Et₂O (5 equiv), CH₂Cl₂, 0 °C to RT, 3.5h; sat NaHCO₃, 80%. X-ray structure of **29** shown in ORTEP format (30% probability thermal ellipsoids, hydrogen atoms omitted for clarity).

Scheme 7.

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

Scheme 8.

Reaction conditions: a) NH₄PF₆ pre-treatment; 5 mol% **31**, 5 mol% 2-(dicyclohexylphosphino)-2'-(*N,N*-dimethylamino)biphenyl, PhMe₂SiH (2.1 equiv), MgI₂ (0.5 equiv), CH₂Cl₂, 55 °C, 18h (**33a+33b:33c** = 4:1, 82%). b) 3 equiv Cy₂BOTf, 4.8 equiv KN(TMS)₂, THF, -78 °C to rt, 20 min. (50%). c) *t*-BuOCl (1.1 equiv), MgX₂ (1.5 equiv), THF / CH₂Cl₂, -78 °C, 2h [when X = Cl: 26% **36** + 8% **35** + 30% **34**; when X = Br: 70% **38**, **37** not detected]. d) Et₃BHLi (5 equiv), toluene, -78 °C (70%). e) TiF₄ (10 equiv), CH₂Cl₂, sealed vial, 80 °C, 30 min. (80%). Structure **33b** has been characterized by X-ray crystallography.

Scheme 9.

Reaction conditions a) NH_4PF_6 pre-treatment; 15 mol% **41**, 17 mol% 2-(dicyclohexylphosphino)-2'-(*N,N*-dimethylamino)biphenyl, PhMe_2SiH (2.1 equiv), LiI (1.1 equiv), CH_2Cl_2 , 55 °C, 72h (82%) (ref 38) b) 2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3,3,3]undecane (10 equiv), $\text{CH}_3\text{CN}/\text{DMF}$, rt, 14h (40%). c) $t\text{-BuOCl}$ (1.2 equiv) CH_2Cl_2 , -78 °C, 1h (20-32%). One diastereomer of **40** has been characterized by X-ray crystallography (ref 17).

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