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A Transient N–O-Linked Pauson–Khand Strategy for the Synthesis of the Deschloro Carbocyclic Core of the Palau'amines and Styloguanidines

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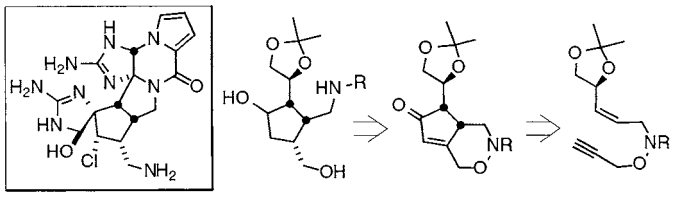
ABSTRACT



A stereocontrolled route to the deschloro cyclopentyl core of the palau'amines and styloguanidines has been developed. This strategy makes use of the intramolecular Pauson–Khand cyclization of an enyne with a "transient N–O tether" to construct a five-membered carbocycle in a diastereoselective fashion.

Guanidine-containing marine natural products display a diverse array of structures and a wide range of biological activity.[1] Both the palau'amines **1** and the regioisomeric styloguanidines **2** are notable members of this class, each containing a bisguanidine moiety, in addition to an immensely complex cyclopentane core. This common motif is stereogenically substituted at every position and includes a quaternary spiro center at C-16 that serves as the locus for one of the two guanidines (Figure 1).[2] Palau'amine **1a** has been shown to display antibiotic, antifungal, and cytotoxic activity, in addition to being a potent immunosuppressant, yet its mechanism of action remains unclear.[2] Furthering our goal of synthesizing the deschloro version of this natural product, we report an intramolecular heteroatom-linked Pauson−Khand mediated assembly of the carbocyclic core of the palau'amines and styloguanidines, providing both

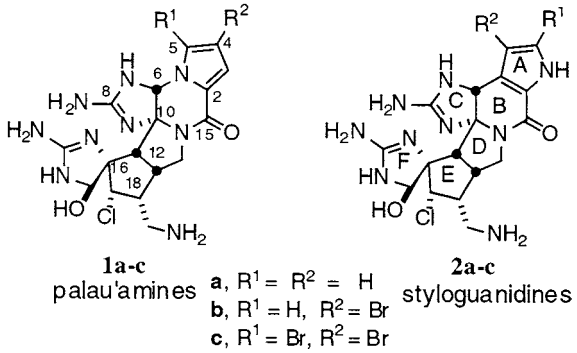


Figure 1. Palau'amines and styloguanidines.

(1) (a) Berlinck, R. G. S. *Nat. Prod. Rep.* **1996**, *13*, 377−409. (b) Berlinck, R. G. S. *Nat. Prod. Rep.* **1999**, *16*, 339−365. (c) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7−55. (d) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1−49. (e) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1−48.

(2) (a) Kinnel, R. B.; Gehrken, H. P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376−7. (b) Kinnel, R. B.; Gehrken, H.-P.; Scheuer, P. J.; Gravalos, D. G.; Faircloth, G. T. *Eur. Pat. Appl.* (Pharma Mar, S. A., Spain). EP 626383, 1994. (c) Kato, T.; Shizuri, Y.; Izumida, H.; Yokoyama, A.; Endo, M. *Tetrahedron Lett.* **1995**, *36*, 2133−6.

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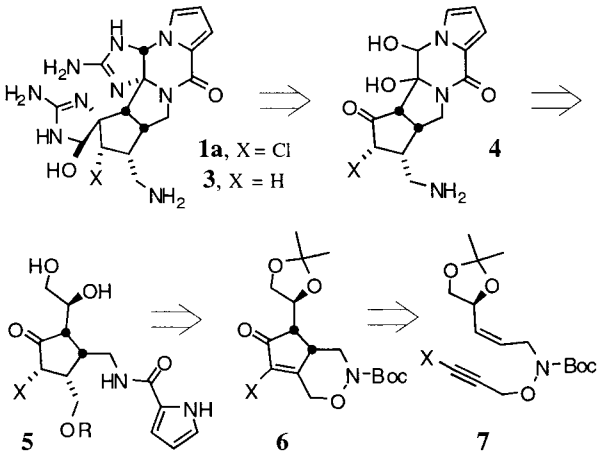
stereocontrolled ring formation and chemical functionality for subsequent manipulation of the core.

Despite much attention in recent years,[3] the palau'amines and styloguanidines have thus far eluded total synthesis. Overman et al. first reported a synthesis of the tetracyclic core of palau'amine using an intramolecular azomethine ylide cycloaddition, with early incorporation of the bisguanidine moiety.[3a,b] Subsequently, two biomimetic Diels−Alder approaches to the palau'amine core were reported, one using 4-vinylimidazoles by Lovely et al.[3c] and a second involving a chlorination/ring contraction, although epimeric at C-17, by Romo et al.[3d] In addition, Carreira et al. described a desymmetrization strategy for the construction of the fully substituted cyclopentane core of axinellamine, a structurally related alkaloid.[3e]

The Pauson−Khand cyclization is a powerful method for the construction of five-member ring carbocycles and has been extensively utilized for the synthesis of natural products.[4] In standing with our interest in the application of the heteroatom-linked Pauson−Khand cyclization,[5] we have devised a stereocontrolled route to the cyclopentyl core of the palau'amines **1a**−**c** and styloguanidines **2a**−**c**, which incorporates an enyne with a "transient N−O tether" as a key intermediate (Scheme 1, **7**).

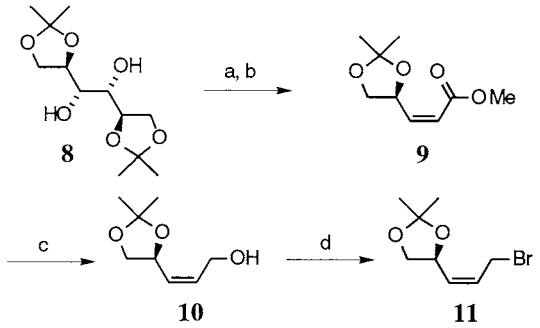
Scheme 1. Retrosynthetic Analysis for the Palau'amine Core



Our approach is based on the observation that these highly functionalized molecules contain a single carbocyclic ring. In our retrosynthetic analysis, we envision a late-stage installation of the bisguanidines from an intermediate such as **4**. This piperazinone diol would be derived from the oxidation and intramolecular cyclization of the pyrrole 2-carboxamide adduct **5**, after N−O cleavage of the Pauson−Khand cyclization product **6**. The key transformation in the synthesis therefore is the intramolecular N−O-linked Pauson−Khand cyclization from enyne **7**, which creates all but one of the required carbon−carbon bonds in the molecule and sets the relative diastereoselectivity about the carbocyclic core. It is important to note at this point that many marine natural products, like palau'amine, contain halogen atoms as an integral part of their structure.[1] In an effort to determine the biological importance of the C-17 chlorine on palau'amine **1a**, our synthetic approach was designed to provide deschloro-palau'amine **3**, while still allowing the future incorporation of the α-chlorine at C-17 for the synthesis of palau'amine itself.

Our synthesis begins with 1,2:5,6-di-*O*-isopropylidene-D-mannitol (Scheme 2, **8**). One-pot periodate cleavage and subsequent Wittig olefination with methyl α-(triphenylphosphoranylidene) acetate under carefully controlled conditions afforded the desired (4*S*)-4,5-*O*-isopropylidenepent-(2*Z*)-enoate **9** with exceptional selectivity (16:1 *Z*:*E* ratio).[6] Since the absolute configuration of palau'amine has not yet been determined, the sugar-derived chirality will allow for convenient reversal of stereoinduction, if necessary. Following reduction with DIBAL-H, the resulting allylic alcohol[7] **10** was converted to bromide **11** by treatment with triphenylphosphine and carbon tetrabromide in acetonitrile.[8] This material serves as the alkene segment of the enyne Pauson−Khand precursor.

Scheme 2. Synthesis of the Chiral Olefin Precursor[a]



[a] Reaction conditions: (a) $NaIO_4$, $NaHCO_3$, 4:1 MeOH/H_2O; (b) methyl α-(triphenyl phosphoranylidene) acetate, −60 → 0 °C (75% for two steps, *Z*:*E* = 16:1); (c) DIBAL-H, CH_2Cl_2, −78 °C (91%); (d) PPh_3, CBr_4, CH_3CN, 0 °C → rt (97%).

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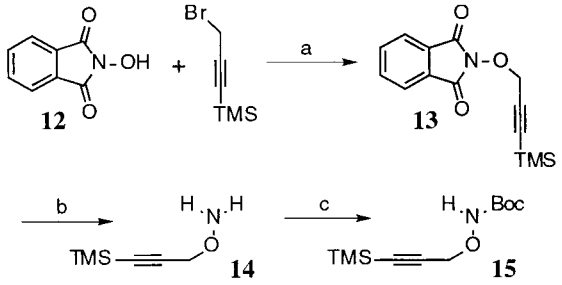
The alkyne moiety is derived from *N*-hydroxyphthalimide (Scheme 3, **12**). Reaction with 3-bromo-1-(trimethylsilyl)-

Scheme 3. Construction of N−O Alkyne[a]

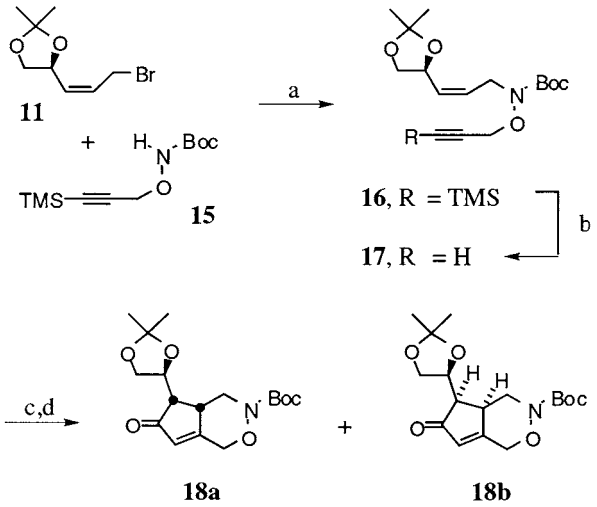


[a] Reaction conditions: (a) DBU, DMF (94%); (b) NH_2NH_2, CH_2Cl_2 (95%); (c) Boc_2O, Na_2CO_3, 1,4-dioxane (79%).

1-propyne gave **13** in 94% yield.[9] Treatment with hydrazine allowed for deprotection of the hydroxylamine **14**. Reprotection with di-*tert*-butyl dicarbonate (Boc_2O) furnished the *N*-alkoxy carbamate **15**.[10] The use of the *tert*-butyl carbamate (Boc) protecting group proved to be the most advantageous for subsequent steps.[11]

Coupling[12] of carbamate **15** with bromide **11** was accompanied by partial loss of the trimethylsilyl group, yielding a mixture of the Pauson−Khand precursors **16** and **17** (Scheme 4). In our model system,[5] the silyl group was found

Scheme 4. Pauson−Khand Cyclization of N−O-Linked Enyne[a]



[a] Reaction conditions: (a) NaH, DMF, 50 °C; (b) K_2CO_3, MeOH, 0 °C → rt (83%); (c) $Co_2(CO)_8$, CH_2Cl_2; (d) Me_3NO, 0 °C → rt (69% for two steps).

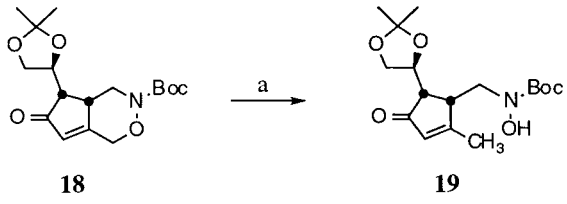
to improve the Pauson−Khand cyclization yields and was also envisaged as an entry point for the chlorine substituent in palau'amine (**1a**). However, preliminary experiments with **16** showed that the TMS group interfered with efficient formation of the cyclopentenone when the acetonide was in place.[11] This is most likely due to the increased steric constraints of the fully elaborated system. Fortunately, the TMS group can be conveniently removed from the alkyne with potassium carbonate (K_2CO_3) in methanol.[13] Treatment of enyne **17** with $Co_2(CO)_8$ in dichloromethane enabled in situ formation of the dicobalt−alkyne complex. Following purging of the system with N_2 and cooling to 0 °C, addition of trimethylamine *N*-oxide (TMANO)[14] provided cyclopentenone **18a** as the major cyclization product in a 4:1 diastereomeric ratio with **18b**.[15]

Optimal results for the Pauson−Khand cyclization are obtained when (1) the glassware is base-washed,[16] rinsed with HPLC-grade water, and oven-dried prior to use; (2) N_2 is bubbled through the solution containing the dicobalt−alkyne complex and the solution is then cooled to 0 °C prior to the addition of TMANO; and (3) the TMANO is added as a dilute solution in dichloromethane.

The (*Z*)-olefin geometry in the Pauson−Khand cyclization provides the syn ring-fusion that is required for the D and E rings of palau'amine. It is also important to note that because the formation of cyclopentenone **18a** proceeds with a diastereomeric preference, based on the chirality derived from D-mannitol, this group can be used as a chiral auxiliary for an asymmetric synthesis of palau'amine since the chiral center of the acetonide will be destroyed during the closure of the pyrrolidine ring (Figure 1, ring D). Once the absolute configuration of natural palau'amine is known, the antipode that provides the correct absolute configuration can simply be chosen from the chiral pool of natural sugars.

While the Pauson−Khand cycloadduct **18** is a pivotal intermediate in our proposed synthetic pathway, cleavage of the N−O bond is equally important since the liberation of each of these heteroatoms is required for completion of the molecule. Initial attempts to cleave the N−O bond, including hydrogenation and use of Na(Hg) amalgam, were unsuccessful. However, treatment of **18**[17] with SmI_2 resulted in formation of the C−O cleavage product **19** in 49% yield (Scheme 5).

Scheme 5. Attempted N−O Bond Cleavage[a]

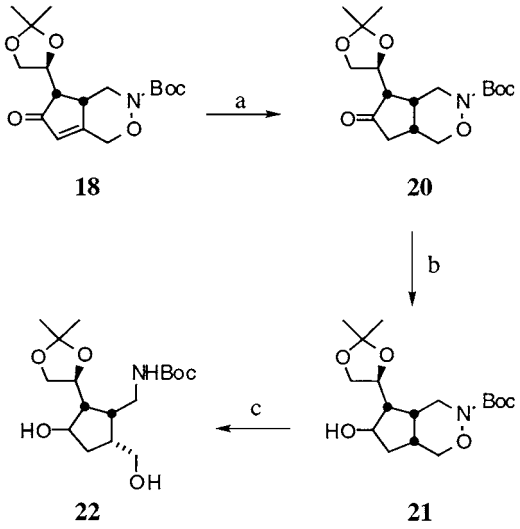


[a] Reaction conditions: (a) 0.1 M SmI_2, THF/EtOH (49%).

This result was unexpected and originally assigned incorrectly.[18] Samarium(II) iodide is known to be an oxophilic one-electron reducing agent, with the ability to form SmI_2−ketyl complexes with carbonyl compounds. These complexes are reactive and have been shown to undergo pinacol[19] and ketone−olefin couplings.[20] In addition, SmI_2 has been

reported to efficiently deoxygenate the α-hydroxy group of aldonolactones in water.[21] Our C−O cleavage reaction is likely a conjugated version of this α-deoxygenation that, while interesting in its own right, is an unwanted byproduct in our synthesis. This reactivity can, however, be suppressed by first reducing the enone prior to treatment with SmI_2. Hydrogenation of **18** in the presence of Pd/C took place in good yield to produce ketone **20** (Scheme 6). Addition of hydrogen from the top face was observed, in keeping with an approach from the less hindered face of the molecule. Reduction of the ketone with lithium borohydride furnished **21** in 80% yield as an inseparable mixture of alcohols. Treatment of alcohol **21** with SmI_2 provided the desired N−O cleavage product **22** in 71% yield. While the need to reduce ketone **20** is unfortunate, this drawback is offset by the facile N−O cleavage and added stability of alcohol **21**. For example, treatment with Na(Hg) amalgam also provides cyclopentanol **22** in 77% yield, conditions that destroyed both ketones **18** and **20**. Additionally, alcohol **22** will be reoxidized during completion of the synthesis, obviating the detrimental effect of the epimeric mixture of alcohols.

Scheme 6. Reduction and N−O Bond Cleavage[a]



[a] Reaction conditions: (a) 57 psi H_2, Pd/C, EtOH (95%); (b) $LiBH_4$, THF, 0 °C (80%); (c) 0.1 M SmI_2, THF/H_2O (71%) or Na(Hg), Na_2HPO_4, EtOH, 0 °C (77%).

In conclusion, we have established a stereocontrolled route to the deschloro cyclopentyl core of the palau'amine and styloguanidine natural products. In addition, a strategy for the selective cleavage of the N−O bond allows efficient liberation of chemical functionality that will be used for the completion of the synthesis. Further elaboration of the molecule toward construction of the complete ring system is currently underway.

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Supporting Information Available: Experimental procedures and characterization data for compounds **10**, **11**, **13**−**15**, and **17**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Although the diastereomeric mixture (**18a**,**b**) was separated for compound characterization (see Supporting Information), **18** was used in subsequent reactions as a mixture of diastereomers. However, only one diastereomer was isolated from each of the transformations (**18**→**19** and **18**→**20**) and the products **19** and **20** correspond to that of the major diastereomer **18a**. For this reason, the diastereochemistry of **18** is depicted as that corresponding to the major diastereomer **18a**.
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