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Total Synthesis of Rhazinilam: Axial to Point Chirality Transfer in an Enantiospecific Pd-Catalyzed Transannular Cyclization

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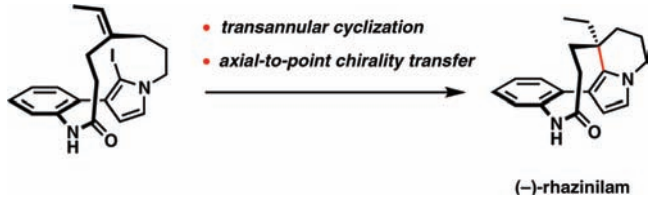
ABSTRACT



A total synthesis of rhazinilam based on a transannular cyclization strategy is described. Using a Heck reaction, the axial chirality of a halogenated 13-membered lactam can be exploited to create the quaternary chiral stereogenic center in the target molecule with high enantiospecificity.

The unusual structure of rhazinilam provided an attractive platform for the development and exploration of new methods and strategies in synthesis. Rhazinilam is characterized by a tetracyclic framework that incorporates a heterobiaryl fragment containing a pyrrole and substituted aniline units, a strained nine-membered lactam, and a quaternary chiral center linked to the pyrrole at the C2-position (Figure 1). Originally isolated from *Rhazya stricta* Decaisne,[1] rhazinilam belongs to a group of natural products that mirror the cellular activity of taxol,[2] generating an additional incentive for their synthesis. It showed inhibition of both microtubule assembly and disassembly in vitro, promoted the formation of abnormal tubulin spirals, and was found to lead to microtubule bundles, multiple asters, and stability of microtubules at low temperatures.[3] Rhazinilam showed

Figure 1. Rhazinilam natural products.

cytotoxicity toward various cancer cell lines at low micromolar range in vitro and no activity in vivo.[3]

The first synthesis of rhazinilam by Smith and co-workers in 1973 relied on an electrophilic aromatic substitution reaction at the C2 position of the protected pyrrole nucleus to install the quaternary stereogenic center (pyrrole number-

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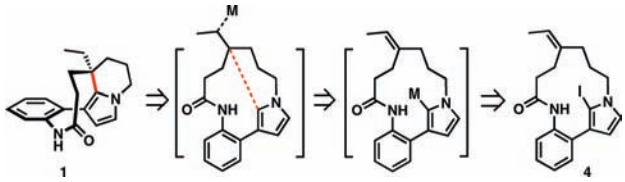
ing).[4] Similar ring-formation order was employed in a number of more recent syntheses, including those highlighting modern C−H-functionalization tactics reported by the groups of Gaunt (rhazinicine),[5] Sames,[6] and Trauner.[7] The synthesis developed by Magnus and Rainey in 2001 illustrates a new method for pyrrole synthesis and avoids the C5-protection of the heterocycle.[8] A gold(I)-catalyzed allene annulation was utilized by the group of Nelson in 2006 to accomplish an enantioselective total synthesis of rhazinilam.[9] In the same year, Banwell and co-workers described the synthesis of (−)-rhazinilam and (−)-rhazinal capitalizing on enantioselective electrophilic pyrrole alkylation under imminium-ion catalysis to form the tetrahydroindolizine fragment.[10]

Strategically, all of these syntheses share a sequential ring-formation approach starting with the assembly of the tetrahydroindolizine ring system and concluding with the formation of the nine-membered lactam.

Considering various options in the synthesis design, we became intrigued by the potential of a transannular cyclization outlined in Scheme 1 to achieve the installation of the

Scheme 1. Transannular Disconnection in the Synthesis of Rhazinilam[a]

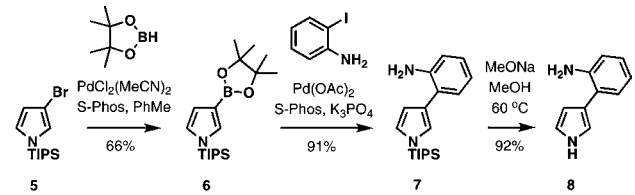


[a] M = transition metal.

quaternary stereogenic center, the nine-membered lactam, and the tetrahydroindolizine ring system in a single bond-forming event. Transannular cyclizations have been recognized as a powerful approach in the synthesis of polycyclic ring systems.[11] A transition-metal-catalyzed process such as a Heck reaction[12] was identified as a preferred method for an initial study of the transannular cyclization, unveiling 13-membered macrolactam **4** as a key precursor. We anticipated that a variety of chiral ligands available for palladium would eventually allow for the development of an enantioselective version of the palladium-catalyzed transannular reaction.[13] In practice, the pursuit of this synthesis plan provided an unexpected insight into the stereochemistry of advanced macrocyclic intermediates offering a distinct approach to enantioselective synthesis of rhazinilam alkaloids in the future.

The synthesis of macrolactam **4** began with the preparation of 2-(1*H*-pyrrol-3-yl)aniline (**8**) following a literature precedent.[14] Borylation of 3-bromo-*N*-triisopropylsilylpyrrole (**5**) with pinacolborane (1.2 equiv) in the presence of bis(acetonitrile)palladium dichloride (3 mol %) and S-Phos (9 mol %) provided boronate **6** (Scheme 2). Cross-coupling

Scheme 2. Synthesis of 2-(1*H*-Pyrrol-3-yl)aniline (**8**)



of **6** with 2-iodoaniline was achieved with the same ligand (S-Phos, 8 mol %), palladium acetate (4 mol %), and potassium phosphate in aqueous 1-butanol in 91% yield. Removal of the triisopropylsilyl group was carried out under basic conditions (MeONa, methanol, reflux) to complete the synthesis of **8** in 92% yield.[15]

The preparation of iodoolefin **13** was initiated by the Michael addition of 2,4-pentanedione to *tert*-butyl acrylate upon treatment with potassium carbonate at 70 °C (Scheme 3). The resulting 1,3-diketone was exposed to aqueous formaldehyde under basic conditions producing enone **10** in 77% yield after a cascade condensation−fragmentation process.[16] Luche reduction ($NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH)[17] followed by acetylation gave **11**, which served as a substrate for subsequent Ireland−Claisen rearrangement forming acid **12** in 71% yield.[18] Selective reduction of **12** followed by iododehydroxylation provided iodide **13** in 79% overall yield.

Preceding the macrolactam formation, a regioselective halogenation at the C2 position of 2-(1*H*-pyrrol-3-yl)aniline (**8**) was required. This type of selective functionalization is useful for the synthesis of a variety of bioactive compounds

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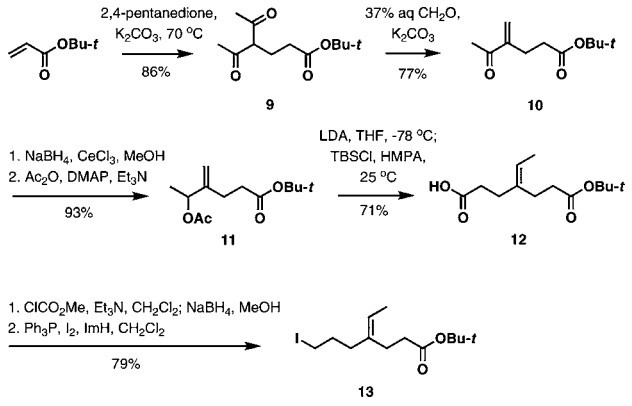
Scheme 3. Synthesis of Iodoolefin **13**



containing a pyrrole subunit; however, only a few examples have been described in the literature. In 2004, a team at Wyeth Research reported a direct bromination at the C2-position of a 3-arylpyrrole with *N*-bromo-succinimide (NBS), although no yields or experimental details were provided.[19] Muchowski and co-workers observed a selective C2-bromination of 3-bromo-1-TIPS-pyrrole upon treatment with 1 equiv of NBS at 23 °C, giving 2,3-dibromo-1-TIPS-pyrrole in a 2.3:1 mixture along with a 3,4-dibromo product.[20] Our experiments began with bromination of **8** with NBS in THF at −78 °C as reported by Wyeth researchers (Scheme 4 and

Scheme 4. Synthesis of Macrocyclic Precursors **20** and **21**

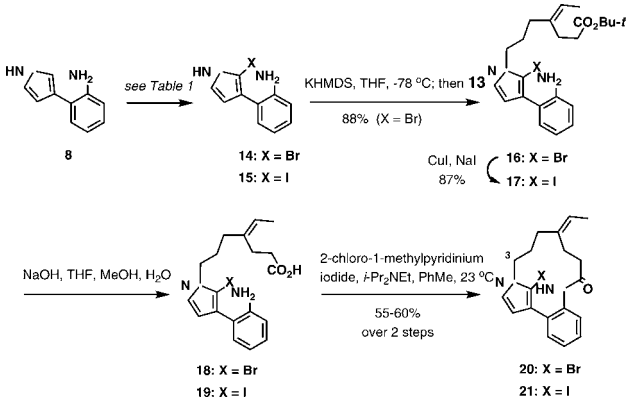


Table 1). These conditions led mostly to unidentified polymeric products. An exposure of **8** to pyridinium tribromide in the presence of pyridine at low temperature also led to decomposition; however, we discovered that when acetic acid was employed as an additive the 2-brominated product **14** was formed selectively and could be isolated in 33% yield. The yields increased with increasing amount of acid, reaching 87% when 3 equiv of trifluoroacetic acid (TFA) was used. These results suggest that acid additives prevent competitive halogenation of the aniline that lead to eventual decomposition. Iodination was explored next, with *N*-iodosuccinimide (NIS) as the source of iodine. While reactions in dichloromethane and THF at 0 °C were not productive, application of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP),[21] which activates NIS and likely stabilizes the product by hydrogen bonding, resulted in a 30% yield of the 2-iodo derivative **15** along with the recovery of the starting material (37%). Addition of TFA, on the other hand, led to decomposition. Iodination with I_2 in the presence of TFA (3 equiv) gave 33% of **15** along with recovery of 55% of the starting material. No complete conversion was achieved even at higher temperatures. Under the optimal conditions, treatment of **8** with NIS in the presence of TFA (3 equiv) in THF at −40 °C smoothly delivered **15** in 88% yield. The only minor byproduct (≤5%) observed in these halogenation reactions was arising from the 2,5-dihalogenation.

Screening of a variety of protocols for macrocyclization indicated that the Mukaiyama reagent, 2-chloro-1-methylpyridinium iodide,[22] was uniquely effective for this operation. The macrolactam ring formation could be carried out at room temperature affording **21** with yields in the range of 55−60% over two steps. No macrocyclic lactam was formed under a variety of conditions using the peptide coupling reagents such as (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU), dicyclohexylcarbodiimide (DCC), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC), 2-methyl-6-nitrobenzoic acid anhydride (MNBA), or 2,4,6-trichlorobenzoyl chloride.[23]

The NMR spectra of lactam **21** indicated that the two protons at the C3 position (Scheme 4, *Aspidosperma* alkaloid numbering) are chemically nonequivalent and thus diastereotopic, revealing that an element of chirality must be present in the structure which can only be attributed to axial chirality. Hence, the iodolactone exists as a mixture of axial enantiomers (R_a)-**21** and (S_a)-**21** (Figure 2). On the other hand, the same protons in the acyclic amino acids **18** and **19** proved to be chemically equivalent at room temperature. Therefore, **18** and **19** do not possess axial chirality (i.e., exist as rapidly interconverting at the NMR time-scale axially chiral conformers).

A number of reagents for enantioselective acylation, including chiral dihydroimidazole reagents **22** and **23** introduced by Birman and Li[24] and Mukaiyama-type reagent **24**, either were not productive in the macrolactamization process or displayed no enantioselection under various reaction conditions when macrolactamization did take place. On the other hand, the enantiomers could be readily separated by preparative chiral HPLC, confirming the existence of axial

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Table 1. Regioselective Halogenation of 2-(1*H*-Pyrrol-3-yl)aniline (**8**)[a]

entry	reaction conditions	yield	entry	reaction conditions	yield
1	NBS, THF, −78 °C	0%	6	$PyH^+ Br_3^-$, THF, TFA, −78 °C	87%[b]
2	$PyH^+ Br_3^-$, Py, THF, −78 °C	0%	7	NIS, THF, 0 °C	0%
3	$PyH^+ Br_3^-$, THF−AcOH (20:1), −78 °C	33%	8	NIS, HFIP, 0 °C	30%[c]
4	$PyH^+ Br_3^-$, THF−AcOH (10:1), −78 °C	46%	9	I_2, TFA, THF, −78 °C	33%[d]
5	$PyH^+ Br_3^-$, THF−AcOH (3:1), −78 °C	51%	10	NIS, TFA, THF, −40 °C	88%[e]

[a] Reported yields are of isolated products. [b] 2,5-Dibromo product was isolated in 4% yield. [c] 37% of the starting material was recovered. [d] 55% of the starting material was recovered. [e] 2,5-Diiodo product was isolated in 5% yield.

chirality in **21** and providing facile access to (R_a)-**21** ($[\alpha]_D^{23}$ −82 (*c* 0.42, CH_2Cl_2)) and (S_a)-**21** ($[\alpha]_D^{23}$ +81 (*c* 0.42, CH_2Cl_2)) in high enantiomeric purity (Figure 2).[25]

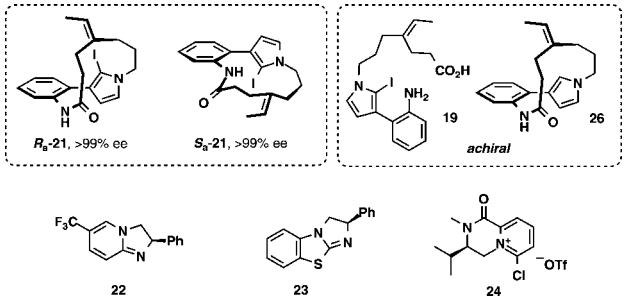
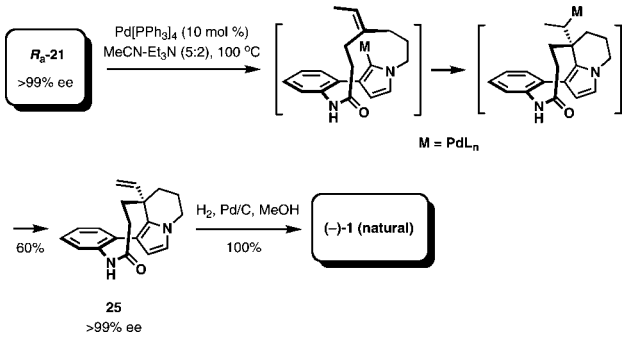


Figure 2. Restricted rotation leads to axial chirality in **21**, but not in **19** and **26**.

Availability of enantioenriched (R_a)-**21** and (S_a)-**21** allowed for examination of the axial-to-point chirality transfer in the penultimate transannular cyclization step (Scheme 5). A requirement for an efficient chirality transfer is that all steps in the projected palladium-catalyzed reaction are enantiospecific.

Scheme 5. Completion of the Total Synthesis of Rhazinilam



As anticipated, when a solution of (R_a)-**21** in acetonitrile was treated with $Pd[PPh_3]_4$ (10 mol %) in the presence of triethylamine at 100 °C,[26] a highly enantiospecific transannular cyclization ensued delivering **25** in 54−64% yield and >99% ee. Hydrodeiodination byproduct **26** was isolated in ∼30% yield. Other combinations of additive ($NaHCO_3$, 1,2,2,6,6-pentamethylpiperidine, *i*-Pr_2NEt, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, quinidine), solvent (DMF, NMP, toluene, THF), and palladium source ($Pd(OAc)_2$, $Pd(dppf)Cl_2$, $Pd(PPh_3)_2Cl_2$, $Pd_2(dba)_3$, Herrmann catalyst, $Pd(OAc)_2$+SPhos, $Pd(OAc)_2$+BINAP) were less effective in this reaction. Under the same reaction conditions, bromide **20** could also be converted to **25**, albeit with a significantly reduced yield (15%) and predominant formation of **26** (75%). Notably, lactam **26** lacking a halogen substituent on the pyrrole ring does not display axial chirality.

Hydrogenation of **25** (H_2, Pd/C, MeOH) produced the natural enantiomer of rhazinilam in quantitative yield. The unnatural (+)-rhazinilam has been prepared in a similar manner from (S_a)-**21**.

In summary, experimental realization of the synthesis strategy based on transannular cyclization to form the ring system of rhazinilam led to the discovery of axial chirality in the macrocyclic cyclization precursors **20** and **21**. This observation allows for the development of enantioselective approaches to rhazinilam alkaloids highlighting axial-to-point chirality transfer in natural products synthesis.

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Supporting Information Available: Experimental procedures and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) The absolute configuration was assigned based on correlation to the final natural product and postulated retention of axial configuration throughout the subsequent transformations.

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