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A New Approach to the Pancratistatin C-Ring from D-Glucose: Ferrier Rearrangement, Pseudoinversion and Pd-Catalyzed Cyclizations

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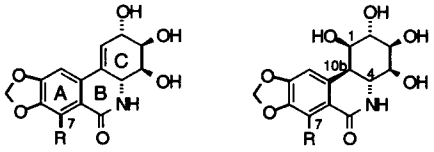
Abstract: A Ferrier rearrangement and β-hydroxyketone transposition are key steps in a route to a pancratistatin C-ring precursor. A key feature of the strategy is the pseudoinversion accomplished by β-hydroxyketone transposition, which allows convenient access from methyl α-D-glucopyranoside. Arylations of the C-ring by intramolecular reductive or non-reductive Pd-catalyzed conjugate addition have been demonstrated, utilizing the C1 hydroxyl to deliver the tethered aryl synthon.

The biological activity, scarcity and structural complexity of Amaryllidaceae alkaloids **1-4** have prompted numerous synthetic studies toward functionalized phenanthridone ring systems,[1,2] including several total syntheses of lycoricidine (**1**). With six contiguous stereogenic centers in their C rings, 7-deoxypancratistatin (**3**) and pancratistatin (**4**) present considerable synthetic challenges, including stereocontrolled introduction of the C10b aryl substituent. Recently, the first successful syntheses of 7-deoxypancratistatin (**3**) and pancratistatin (**4**) have been reported.[3,4,5]

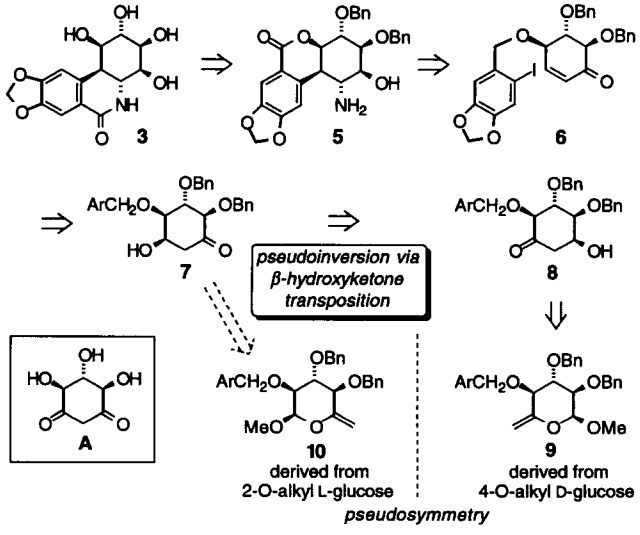


1 (R = H)
2 (R = OH)

3 (R = H)
4 (R = OH)

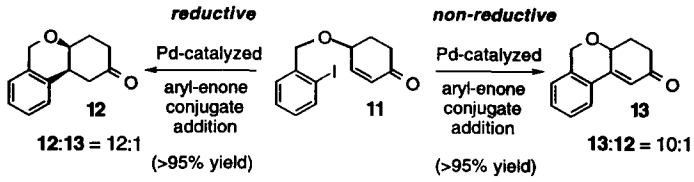
Our efforts in this area focused on a synthesis of 7-deoxypancratistatin (**3**) which would be capable of general access to highly oxygenated members of the phenanthridone alkaloids, including (+)-pancratistatin (**4**). Notable features of our strategy (Scheme 1) include the utilization of the C1 β-hydroxyl to deliver a tethered aryl synthon to the β face at C10b resulting in a cis-fused ring system, subsequent electrophilic enolate amination on the convex face, and an endgame based on a lactone → lactam isomerization (**5** → **3**).[6]

Scheme 1



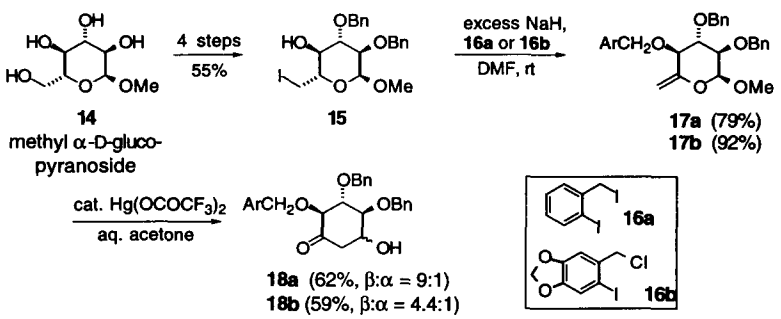
To support the development of the strategy shown in Scheme 1, we recently described model studies of intramolecular palladium-catalyzed aryl iodide-enone conjugate addition reactions of 4-iodobenzyloxycyclohexenone **11** to selectively form tricyclic arylation products **12** or **13** (Scheme 2).[7] Importantly, the reductive cyclization product **12** was formed with *complete selectivity for the cis ring junction as required for pancratistatin synthesis* (>95% by ^{1}H NMR spectroscopy, no trans product detected); these results encouraged us to pursue the application of this stereoselective arylation reaction to the synthesis of 7-deoxypancratistatin (**3**).

Scheme 2



Our strategy for the synthesis of **3** required the highly oxygenated cyclohexenone **6**. A enantiopure source of the asymmetry in **6** is a pyranose sugar, with a Ferrier carbocyclization to convert the pyran to a cyclohexanone. However, the standard Ferrier retrosynthetic disconnection leads to the 2-O-alkyl L-glucoside **10** (or an analogous 2-O-alkyl-D-idoside). We recognized a plane of symmetry in hypothetical diketone **A**; the corresponding plane through Ferrier rearrangement products **7** and **8** suggests a pseudosymmetrical relationship which could be exploited to circumvent a tedious differentiation of the C2 from C3 and C4 hydroxyls of expensive L-glucose or D-idose.[8] Thus, we would effect pseudoinversion of a D-glucose derivative to its L-glucose (or D-idose) counterpart by transposing the β-hydroxyketone moiety; the requisite 4-O-alkyl-D-glucose-derived precursor **9** is readily available from inexpensive methyl α-D-glucopyranoside.

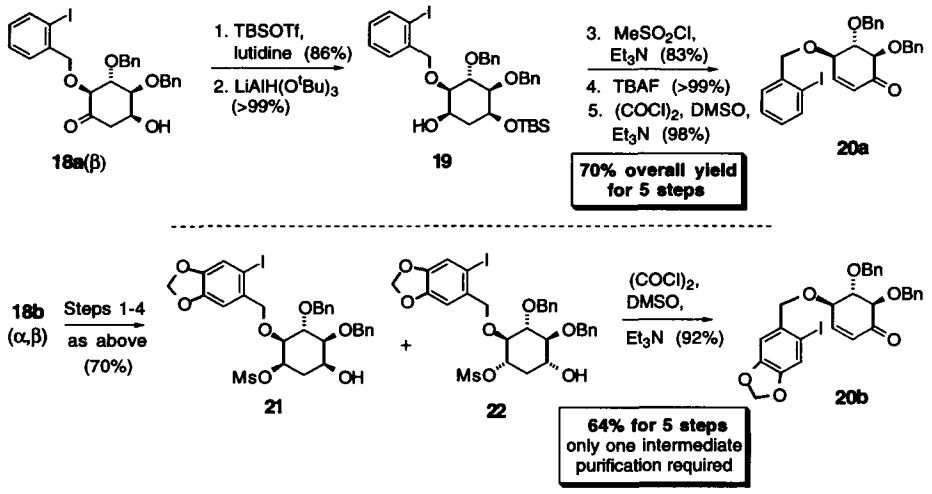
Scheme 3



Starting from methyl α-D-glucopyranoside (**14**), known 6-iodo-6-deoxy-α-D-glucopyranoside **15**[9] was prepared by a 4-step sequence in 55% overall yield. As shown in Scheme 3, treatment of iodide **15** with excess NaH and either 2-iodobenzyl iodide (**16a**) or 6-iodo-3,4-methylenedioxybenzyl chloride (**16b**)[10] in DMF both alkylated the C4 hydroxyl and eliminated HI at C5 and C6,[11] forming hexenopyranosides **17** (**17a**: 79%; **17b**: 92%). Ferrier rearrangement (catalytic $Hg(OCOCF_3)_2$, 4:1 acetone/H_2O, rt)[12] of the hexenopyranosides provided mixtures of diastereomeric β-hydroxyketones **18** (**18a**: β:α = 9:1 (62%); **18b**: β:α = 4.4:1(59%)). In each case the α,β epimers could be separated by crystallization.

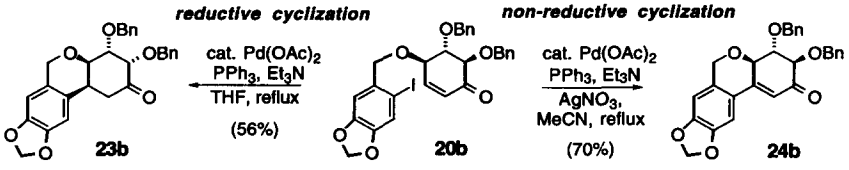
Transposition of the β-hydroxyketone functionality of **18a**(β) was achieved using a simple and efficient five-step protocol (Scheme 4). Silyl protection (TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 86%)[13] and reduction of the ketone under aprotic conditions ($LiAlH(O^tBu)_3$, THF, rt, >99%)[14] afforded a single diastereomer **19**, which was converted to a methanesulfonate ester (MsCl, Et_3N, CH_2Cl_2, rt, 83%). Fluorodesilylation (TBAF, THF, rt, >99%) cleanly furnished a β-hydroxyalkyl mesylate (not shown). To our good fortune, both hydroxyl oxidation and mesylate elimination occurred smoothly in one step under Swern oxidation conditions[15] (DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C; then Et_3N, rt; 98%), yielding the key cyclization precursor **20** with a 70% overall yield for the five-step pseudoinversion/elimination sequence.

Scheme 4



In the more highly oxygenated series, the major Ferrier rearrangement product **18b**(β) could be converted to cyclization substrate **20b** by the 5-step transposition/elimination sequence described above, but in practice it was convenient and efficient to employ the α,β diastereomeric mixture of Ferrier products **18b**(α,β) since the stereochemistry at the epimeric center was removed by alcohol oxidation. Thus, silylation, reduction, mesylation, and desilylation were conducted as described above, producing only diastereomers **21** and **22** in 70% yield for 4 steps.[16] Swern oxidation was performed on mixtures of **21** and **22** in 92% yield, giving an overall 64% yield of cyclization precursor **20b** in 5 steps for the pseudoinversion/elimination sequence from **18b**(α,β). Notably, this convenient sequence was performed without intermediate purifications (beyond aqueous workup) until just prior to Swern oxidation.

Scheme 5



We were able to conduct intramolecular Pd-catalyzed conjugate addition reactions of **20a** and **20b** (Scheme 5, **20a** series not shown) to selectively afford either reductive cyclization products or non-reductive products.[17] Preparative scale (ca. 1 g) experiments afforded good isolated yields of either **23b** (56%) or **24b** (70%) using these conditions. We were delighted to observe that the reductive conditions were *completely selective for the desired cis ring junction*, as required for our synthesis of 7-deoxypancratistatin. Unfortunately, X-ray crystallographic analysis of **23b** revealed that a remote epimerization had occurred to invert the configuration at the α-benzyloxyketone.[18] We speculate this is attributable to the relief of 1,3-diaxial steric interactions between the α-benzyloxy substituent and the cis-fused benzopyran ring. We envision that suppression of the unanticipated epimerization which forms **23b**, or the stereoselective conjugate reduction of **24b**, which did not suffer the remote epimerization, will allow continued progress toward synthesis of 7-deoxypancratistatin and analogs.

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10. Benzylic alkylating agent **16b** was prepared in two steps by aromatic iodination of commercially available piperonyl alcohol (I_2, $Ag(OOCCF_3)_2$, 78%) and conversion to the benzylic chloride ($MeSO_2Cl$, Et_3N, 87%); this was closely related to the procedure of Overman et al., see: Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959.
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14. Reduction with $NaBH_4$ in ethanol was complicated by base-induced enolization and subsequent elimination of BnOH.
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16. That only **21** and **22** were obtained demonstrated that **18b**(α) and **18b**(β), after silylation, each underwent highly stereospecific hydride reduction. Chromatographically separated **21** and **22** each furnished **20b** upon Swern oxidation in parallel experiments.
17. Product ratios of crude product mixtures were obtained by integration of ^1H NMR spectral data: For reductive cyclization, **23a**:**24a** = 4:1 and **23b**:**24b** = 5:1. For non-reductive cyclization, **24a**:**23a** = 9:1 and **24b**:**23b** = 12:1. Details are found in reference 7.
18. This epimerization was not discernible by ^1H NMR coupling constant analysis. Prior to crystallographic analysis, we had misassigned this structure in an earlier communication (see reference 7).

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