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A Concise Route to Enantiomerically Pure 2-Arylcyclohexenones of Relevance to the Pancratistatin Problem

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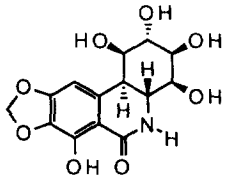
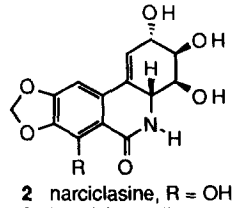
Summary: A transformation involving a 6-aryl "exo" glycal is used to prepare the target structures from carbohydrate starting materials.

To date only one total synthesis of pancratistatin (**1**) has been reported.[1] While this synthesis successfully dealt with several interesting stereochemical problems, it was quite lengthy and it was not well suited toward producing the natural enantiomer. Pancratistatin and its congeners (cf. narciclasine (**2**) and lycoricidine (**3**)) are potential antitumor agents.[2a,b] We as well as others have been investigating alternative more concise strategies to reach the phenanthridone family of alkaloids in the natural enantiomeric series.[2c-2g]

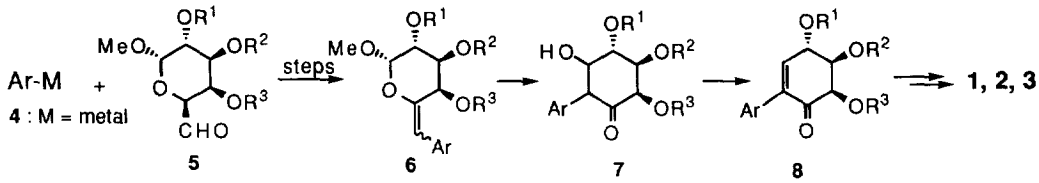


1 pancratistatin



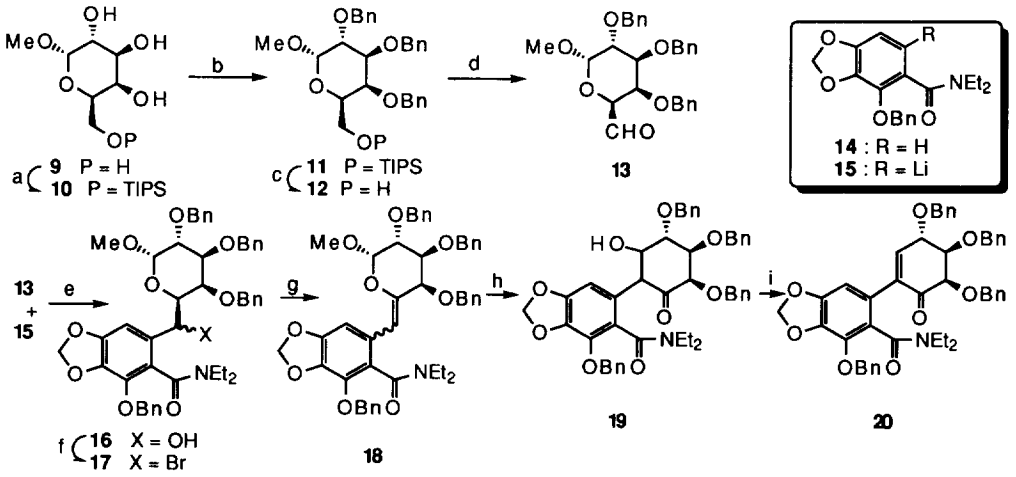
2 narciclasine, R = OH
3 lycoricidine, R = H

We sought to extend the Ferrier rearrangement[3] to the case of 6-aryl-$\Delta^{5,6}$-pyranosides (exo glycals) as a route to 2-arylcyclohexenones bearing pertinent oxygens in the cyclitol sector. The sequence **6**—>**7**—>**8** presented itself. Precursor **6** might be fashioned from ulose **5** and aryl lithium species **4**. The encouraging results of our opening feasibility inquiry are related in this Letter.



5 **6** **7** **8**

The synthesis started with methyl-α-D-galactopyranoside (**9**). Protection of the primary alcohol as the TIPS ether was followed by per-benzylation to afford **11** and thence alcohol **12**. Oxidation of **12** gave the desired ulose **13**. The particular version of **4** selected for our purpose was **15**, prepared by a Snieckus ortho-lithiation[4] of **14**, previously described in our total synthesis. Reaction of **13** with **15** gave a 2:1 mixture of diastereomers **16**, in 50-70% yield. A variety of attempts to achieve direct dehydration of **16**—>**18** were unsuccessful.



a) TIPSCl, Imid., DMF, 85%: b) NaH, BnBr, DMF, 84%: c) TBAF, THF, 95%: d) Swern oxid. 96% : e) **14**, s-BuLi, TMEDA, THF, -78°, then **13**, 50-70%: f) Ph_3PBr_2, K_2CO_3, CH_2Cl_2, 75%: g) pyridine, reflux, 2h, 75%: h) $HgCl_2$, H_2O-acetonitrile (1:2), reflux, 70-80%: i) Ac_2O, DMAP, Pyridine, 70%

However, conversion of **16** to bromide **17** was possible as shown. Heating of **17** in dry pyridine did indeed afford **18** as an E,Z mixture in 75% yield. Subjection of **18** to classical Ferrier conditions afforded **19** as well as small amounts of **20**. The conversion of **19**—>**20** was achieved with acetic anhydride in pyridine. Thus a concise route to a 2-arylcyclohexenone, appropriately functionalized and configured to reach various phenanthridone alkaloids, has been demonstrated.

The advancement of compound **20** itself toward pancratistatin is complicated by difficulties of manipulating the N,N-diethylamide group in the presence of the sensitive resident functionality. Modifications of the protecting groups for the coupling process as well as for the double bond introduction and Ferrier steps are being pursued.

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References and Notes

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