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An Approach to the Narciclasine Alkaloids via a Quinone Methide Initiated Cyclization Reaction

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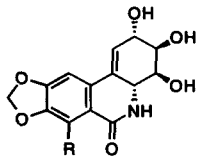
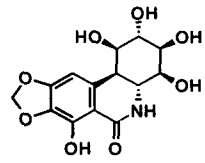
Abstract: The stereoselective synthesis of a possible intermediate for the synthesis of the narciclasine alkaloids from *D*-glucose is described. The key step of the sequence is a quinone methide initiated cyclization reaction. © 1997 Elsevier Science Ltd.

The *Amaryllidaceae* alkaloids are a group of plant-derived natural products which include the powerful antimitotic agents, narciclasine (**1**),[2] lycoricidine (**2**),[3] and pancratistatin (**3**).[4] All three compounds have been the subject of extensive synthetic investigations.[5-8] We have reported a previous approach to these alkaloids[6f] and report here the refinement of our quinone methide initiated cyclization strategy for the synthesis of a highly functionalized nitrocyclitol derivative.



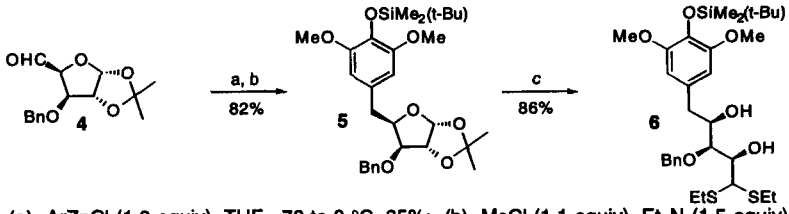
1, Narciclasine; R = OH
2, Lycoricidine; R = H



3, Pancratistatin

The known aldehyde **4** was transformed to acetonide **5** in 82% yield using a modification of our previously reported route (Scheme 1).[6f,9] In our earlier work, we had found the acetonide of **5** to be robust, and strong acid (6 *N* H_2SO_4 or HNO_3) was required to remove this protecting group.[6f] In an effort to effect this deprotection under milder conditions, we examined Kim's procedure for MOM-ether cleavage.[10] Treatment of **5** with excess ethanethiol and magnesium bromide afforded thioacetal **6** in 86% yield.[9]

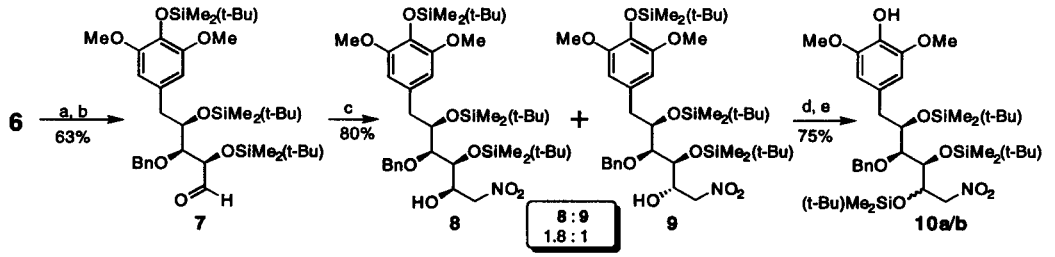
Scheme 1.



(a) ArZnCl (1.8 equiv), THF, -78 to 0 °C, 85%; (b) MsCl (1.1 equiv), Et_3N (1.5 equiv), ether, 0 °C, 30 min; $LiAlH_4$, 0 °C to rt, 20 min, 97%; (c) EtSH (10 equiv), $MgBr_2{\cdot}OEt_2$ (10 equiv), ether, 0 °C to rt, 21 h, 86%.

Protection of diol **6** as the bis-TBDMS ether followed by hydrolysis of the thioacetal afforded aldehyde **7** in 63% overall yield (Scheme 2).[11] Nitro aldol reaction of **7** with nitromethane afforded **8** and **9** as an inseparable mixture of diastereomers (1.8:1 ratio, ^{1}H NMR) in 80% yield.[12] Attempts to improve the diastereoselectivity by changing the counterion (Li, Na), or the addition of Lewis acids ($MgBr_2$, $ZnCl_2$, $SnCl_2$) failed to provide material in good yield and/or selectivity. For example, reaction of **7** with *t*-BuOK in THF with 1 equiv of $MgBr_2$•Et_2O (3 days, rt) afforded **8** and **9** in an improved 2.5:1 ratio, but the yield was only 14%. Attempts to force the reaction to completion resulted in intractable product mixtures. The stereochemistry of **8** and **9** was assigned by conversion to **12** and **13** (vide infra). Treatment of the **8/9** mixture with excess TBDMS-OTf resulted in silylation of the alcohol and the nitro group. Flash chromatography on silica gel (10:1 hexanes/ethyl acetate) effected hydrolysis of the silylnitronic ester to afford the protected alcohol in 95% yield. Selective deprotection of the phenolic TBDMS ether was achieved by treatment with camphorsulfonic acid in methanol to afford **10a/b** (1.8:1 mixture) in 79% yield.[9]

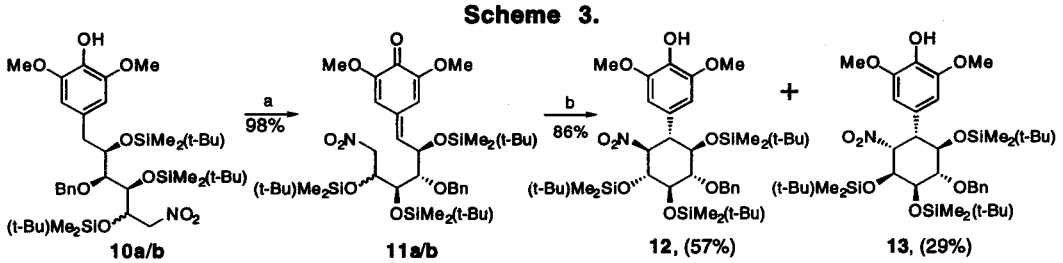
Scheme 2.



(a) TBDMS-OTf (2.9 equiv), 2,6-lutidine (3.0 equiv), CH_2Cl_2, 0 °C 15 min then rt 2 h, 79%; (b) $HgCl_2$ (4 equiv), HgO (5 equiv), CH_3CN/H_2O 10:1, rt, 1 h, 80%; (c) CH_3NO_2, (10 equiv), *t*-BuOK (1 equiv), THF, 0 °C 45 min, 80%; (d) TBDMS-OTf (4 equiv), 2,6-lutidine (10 equiv), CH_2Cl_2, 0 °C 30 min then rt 67 h; flash chromatography, 95%; (e) CSA (0.4 equiv), MeOH, rt, 4 h, 79%.

Oxidation of phenols **10a/b** with silver(I) oxide[13] afforded quinone methides **11a/b** (Scheme 3). The stage was now set for the key quinone methide cyclization. After a brief survey of bases (Et_3N, NaH, DMAP), 4-(dimethylamino)pyridine was found to be the optimal base for effecting the cyclization of the quinone methides. Treatment of a methylene chloride solution of **11a/b** (1.8:1 mixture of diastereomers) with DMAP afforded **12** and **13** in 57% and 29% yield respectively.[13] The ratio of **12** to **13** was 2:1, remarkably close to the ratio of the starting diastereomers, 1.8 to 1. The combined yield of **12** and **13** after chromatography was 86%, showing the quinone methide initiated cyclization to be an efficient and stereospecific process.

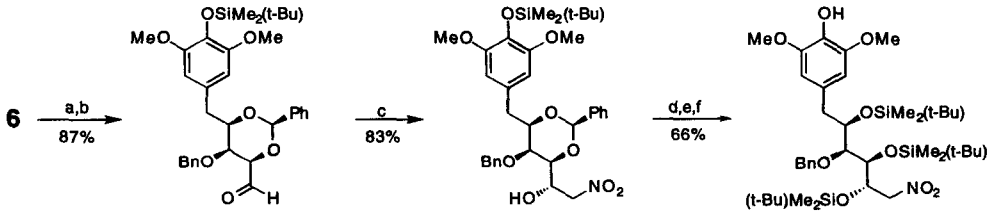
Scheme 3.



(a) Ag_2O (5 equiv), ultrasound, $CDCl_3$, 22-55 °C, 14 h, 98%; (b) DMAP (5 equiv), CH_2Cl_2, rt, 5 h, 86%.

The minor cyclization product, **13** possesses five of the six stereogenic centers of pancratistatin in their correct relative and absolute configuration. Unfortunately, **13** was the *minor* diastereomer obtained in the cyclization. It seemed likely that **11b** afforded **13**, the desired product and that a stereoselective route to **11b** would result in exclusive formation of **13**. As mentioned above, attempts to improve the stereoselectivity of the nitro aldol reaction of **7** failed. In an effort to change the environment about the aldehyde, and hopefully improve the stereoselectivity of the nitro aldol reaction, **6** was converted to the corresponding benzylidine acetal by reaction with benzaldehyde dimethylacetal. Selective hydrolysis of the thioacetal[11] afforded aldehyde **14** (Scheme 4). Nitro aldol reaction of **14** afforded a single adduct, **15** in 83% yield and >99:1 diastereoselectivity. Treatment of **15** with ethanethiol and stannous chloride effected removal of the benzylidine acetal without dehydration of the β-hydroxynitro functionality to afford a triol in 82% yield. Protection of the triol with excess TBDMS-OTf afforded a 91% yield of the corresponding TBDMS ether. Selective removal of the phenolic TBDMS group was effected by treatment with camphorsulfonic acid in methanol to afford **10b** in 88% yield. Phenol **10b** prepared by this route was identical to **10b** found in the **10a/10b** mixture that was prepared from **7**. Thus by simply adjusting the protecting group on the diol, a stereoselective route to **10b** was realized with only one additional step.

Scheme 4.

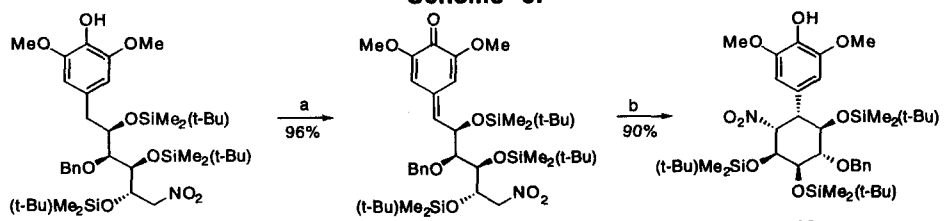


14 **15** **10b**

(a) $(MeO)_2CHPh$ (5 equiv), CSA (0.2 equiv), C_6H_6, rt, 20 min, (100%); (b) $HgCl_2$ (4 equiv), HgO (5 equiv), CH_3CN/H_2O 10:1, rt, 20 min, 87%; (c) CH_3NO_2, (10 equiv), *t*-BuOK (1 equiv), THF, 0 °C, 35 min, 83%; (d) EtSH (10 equiv), $SnCl_2$ (1.0 equiv), CH_2Cl_2, rt, 20 h, 82%; (e) TBDMS-OTf (7 equiv), 2,6-lutidine (8 equiv), CH_2Cl_2, 0 °C to rt, 44 h, 91%; (f) CSA (0.4 equiv), MeOH, rt, 4 h, 88%.

Oxidation of **10b** with silver(I) oxide[13] afforded quinone methide **11b** in 96% yield (Scheme 5). Treatment of **11b** with DMAP afforded **13** as the sole cyclization product in 90% yield, thereby showing that the cyclization of **11a** and **11b** was indeed stereospecific. The structure assignments for **12** and **13** are based on ^1H NMR coupling constants and NOE-difference spectra.

Scheme 5.



10b **11b** **13**

(a) Ag_2O (5 equiv), ultrasound, $CDCl_3$, 24-57 °C, 14 h, 96%; (b) DMAP (5 equiv), CH_2Cl_2, rt, 3.5 h, 90%.

In summary, we have prepared nitrocyclitol **13** from *D*-glucose derived aldehyde **4** in 11 steps and 29% overall yield. This work demonstrates the versatility of a quinone methide-based pathway for the synthesis of the narciclasine alkaloids. Studies to exploit this route are currently under investigation.

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