Pergamon

Tetrahedron Letters, Vol. 38, No. 46, pp. 7955-7958, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10138-1

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

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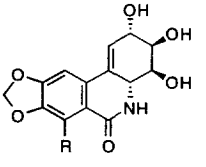
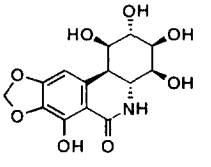
Abstract: The stereoselective synthesis of a possible intermediate for the synthesis of the narciclasine alkaloids from *D*-glucose is described. The key step of the sequence is a quinone methide initiated cyclization reaction. © 1997 Elsevier Science Ltd.

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.



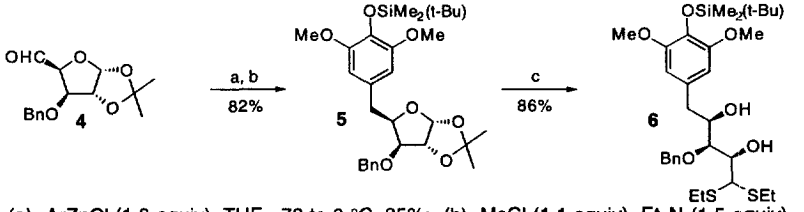
1, Narciclasine; R = OH
2, Lycoricidine; R = H



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]

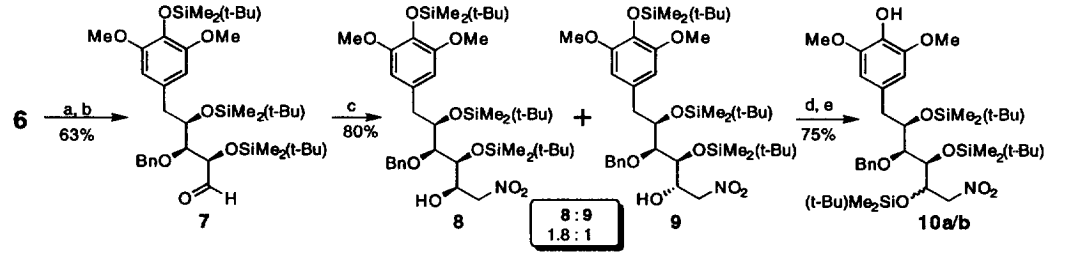
Scheme 1.



(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), $MgBr_2$•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]

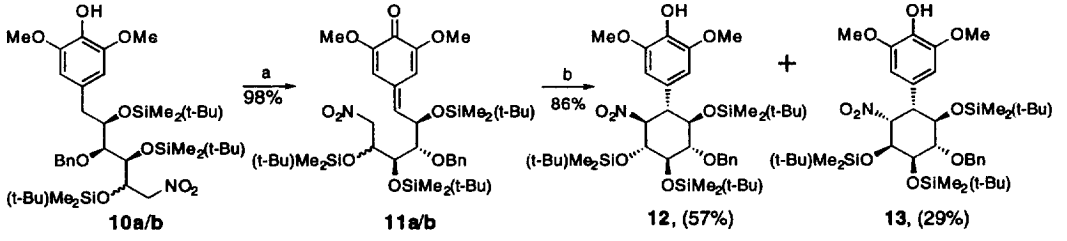
Scheme 2.



(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.

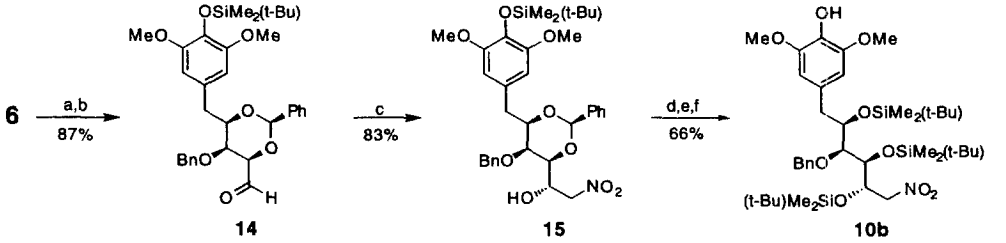
Scheme 3.



(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.

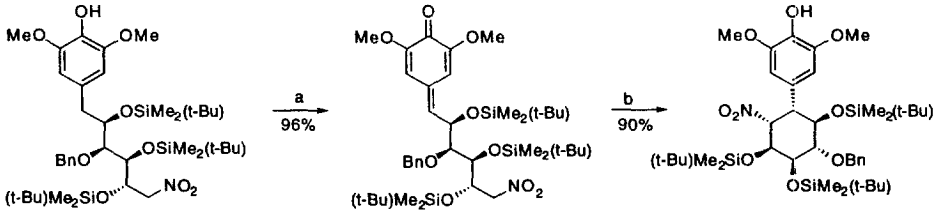


14 **15** **10b**

(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.

Acknowledgments: We would like to thank Dr. Azad Hossain, Dr. Young Kwan Ko, Dr. Michael Louie, Mr. Robert M. Henry and Mr. Musong Kim for initial work on this project. Acknowledgment is made to the NIH (GM39354), Showa Denko K.K. and the Alfred P. Sloan Foundation (fellowship to SRA) for support of this research.

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(*Received in USA* 11 *August* 1997; *accepted* 8 *September* 1997)