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A Convenient Synthesis of C-22 and C-25 Stereoisomers of Cephalostatin North 1 Side Chain from Spirostan Sapogenins

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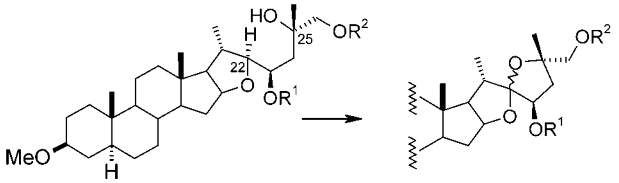
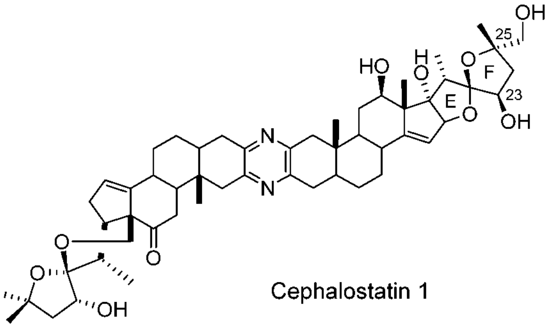
ABSTRACT



A simple transformation of the eight-carbon side chain of a natural spirostan sapogenin into the cephalostatin north 1 spiroketal moiety is described. This methodology, based on an intramolecular hydrogen abstraction reaction promoted by alkoxy radicals, permits the synthesis of C-22 and C-25 stereoisomers of the dioxaspiro[4.4]nonane cephalostatin ring system. The acid-catalyzed isomerization of the spirocenter in the different isomers is studied.

Several marine alkaloid cephalostatins[1] and ritterazines[2] are among the most potent cytotoxins ever isolated from a natural source.[3] They are formed by two steroidal units linked through a pyrazine ring involving C2 and C3 of each monomeric unit. In most of the cephalostatins (17 out of 19) the north steroidal eight-carbon side chain has been transformed into a polyoxygenated (2*S*,4*R*,5*S*,9*S*)-2-hydroxymethyl-2,9-dimethyl-1,6-dioxaspiro[4.4]nonan-4-ol substructure (see, for example, cephalostatin 1).



Cephalostatin 1

Their unique structure and biological activity have made them an important synthetic target. The syntheses of several

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(2) Recent publication: Fukuzawa, S.; Matsunaga, S.; Fusetani, N. *J. Org. Chem.* **1997**, *62*, 4484−4491 and references therein.

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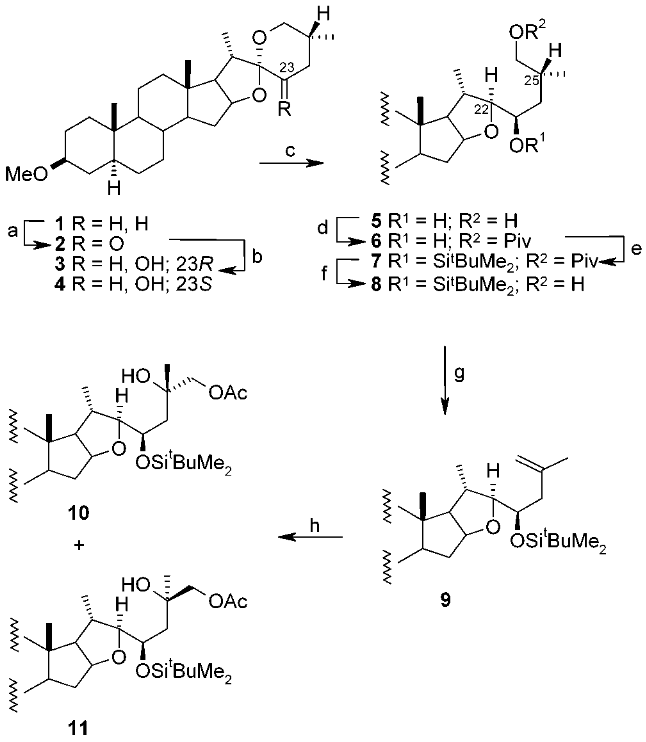
of these natural products and analogues have been achieved,[4] but despite efforts by several research groups, the mechanism of action of these compounds remains unknown.[5]

Taking into account the SAR correlation of cephalostatins and OSW-1,[6] a related cholestane glycoside isolated from a terrestrial plant, it was hypothesized that the active intermediate might be an oxycarbenium ion located at rings E or F and originated by opening of the dioxaspiro grouping.[7] We can deduce from this that the stereochemistries at C-22, C-23, and C-25, which doubtless have a strong influence on the stability of the dioxaspiro[4.4]nonane system, may also influence the activity of cephalostatins.

With these ideas in mind, we decided to develop a simple methodology to permit the synthesis of all possible isomers of this system by modification of the steroidal side chain of a spirostan sapogenin, the key step being an intramolecular hydrogen abstraction reaction (IHA) promoted by alkoxy radicals.[8] In previous papers from this laboratory, we have demonstrated the utility of IHA reactions in the synthesis of dioxaspiro[4.4]nonane ring systems in the carbohydrate field.[9]

The synthesis starts with 3-methoxy-23-oxotigogenin (**2**) (Scheme 1) prepared using a previously described procedure by oxidation of 3-methoxytigogenin (**1**) with NaNO$_2$/BF$_3$·Et$_2$O.[10] The reduction of **2** with L-Selectride gave a mixture of alcohols **3** and **4** (72%, 1.7:1) from which the alcohol **3** with the correct natural orientation (23*R*) could be obtained in moderate yield. The reduction of **2** with NaBH$_4$ afforded preferentially the non-natural isomer **4** (91%, 19:1). In these preliminary studies we decided to continue with the natural diastereoisomeric alcohol **3**. The regio- and stereoselective opening reaction of the tigogenin dioxaspiro[5.4]decane system present in **3** was accomplished with Ph$_2$SiH$_2$/TiCl$_4$ to give diol **5** in 67% yield.[11]

Scheme 1[a]



[a] Reagent and conditions: (a) NaNO$_2$, BF$_3$·Et$_2$O, AcOH, rt, 1 h, 68%; (b) NaBH$_4$, EtOH, rt, 1 h, 91% (**3**/**4** ratio 5:95) or L-Selectride, THF, −20 °C, 2 h, 72% (**3**/**4** ratio 63:37); (c) Ph$_2$SiH$_2$, TiCl$_4$, CH$_2$Cl$_2$, −20 °C, 1.5 h, 67%; (d) pivaloyl chloride, Py, CH$_2$Cl$_2$, rt, 24 h, 96%; (e) ^{t}BuMe$_2$SiOTf, CH$_2$Cl$_2$, Et$_3$N, rt, 3 h, 81%; (f) KOH, MeOH, 50 °C, 24 h, 92%; (g) (i) *o*-NO$_2$PhSeCN, *n*-Bu$_3$P, THF, rt, 0.5 h, 99%, (ii) H$_2$O$_2$, THF, rt, 3 h, 92%; (h) (i) OsO$_4$, Py, CH$_2$Cl$_2$, rt, 1.5 h, (ii) Ac$_2$O, py, rt, 99% (**10**/**11** ratio 1:2).

Conversion of **5** to the monoprotected primary alcohol **8** was accomplished by a protection−deprotection sequence involving formation of the primary pivalate **6** (96%), silylation with TBSOTf (81%), and hydrolysis of pivalate **7** with KOH/MeOH (92%). Nitrophenylselenenylation of the primary alcohol in **8** followed by oxidative elimination furnished alkene **9** in 92% yield. Osmylation of the double bond and subsequent acetylation afforded tertiary alcohols **10** and **11** (99%, 1:2).[12]

The IHA reaction was carried out by separately treating compounds **10** and **11** with (diacetoxyiodo)benzene and iodine under irradiation with two 80 W tungsten-filament lamps at 50 °C. Alcohol **10** afforded a mixture of the dioxaspirocycles **12** and **13** (83%, 28:72) while alcohol **11** gave compounds **17** and **18** (83%, 33:67) (Scheme 2). The desired diols **14**, **15** and **19**, **20** (Scheme 2) were subsequently obtained by hydrolysis of the silyl and acetate protective groups, the structures of which were determined by extensive ^{1}H and ^{13}C NMR 1D and 2D studies including DEPT, COSY, HMBC, HSQC, and NOESY experiments and confirmed by X-ray crystallography analysis of compounds **15** and **20**. The

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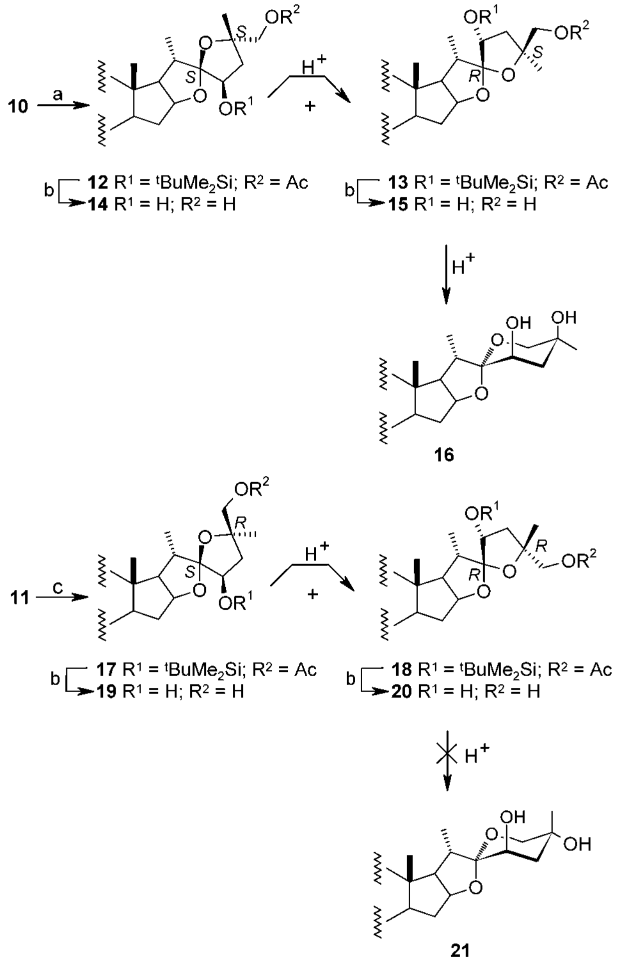
(12) For studies on the diastereoselective osmylation of a related olefin see: refs 4b,c.

Scheme 2. IHA Reaction from Compounds **10** and **11**[a]



[a] Reagents and conditions: (a) $PhI(OAc)_2$, I_2, cyclohexane, *hν*, 50 °C, 3.5 h, 83% (**12**/**13** ratio 28:72); (b) (i) TBAF, THF, rt, (ii) KOH, MeOH, rt; (c) $PhI(OAc)_2$, I_2, cyclohexane, *hν*, 55 °C, 7 h, 83% (**18**/**19** ratio 33:67).

(22*S*,23*R*,25*S*)-diol **14** possesses the stereochemistry of the natural product. Compounds **14** and **19** appear to be the products of kinetic control whereas **15** and **20** are the thermodynamic products. The stability of these compounds was determined by following the evolution of the acid-catalyzed rearrangement through a C-22 oxycarbenium ion. Compound **14** was transformed into the 22*R*-isomer **15** and both **14** and **15** finally led to the dioxaspiro[4.5]decane **16** under prolonged hydrochloric acid treatment (Scheme 2).[13] In the 25*R* series the equilibrium is also strongly displaced from the 22*S*-diol **19** toward the more stable 22*R*-compound **20**. One interesting observation was that even under prolonged reaction time neither **19** nor **20** yielded the corresponding dioxaspiro[4.5] compound **21** to any appreciable extent, in contrast to the series possessing the natural stereochemistry. These findings are in agreement with the results of a MM2 study,[14] compounds **14** and **19** being the highest steric energy isomers in the respective series while compounds **15** and **20** are more stable ($\Delta E_{\mathbf{14,15}} = 5$ kcal/mol; $\Delta E_{\mathbf{19,20}} = 2.6$ kcal/mol).

In conclusion, we have prepared four of eight possible isomers of the target molecule and their reactivity toward acid catalysts has been studied. The usefulness of the IHA reaction to construct the different stereoisomers of this steroidal dioxaspiro[4.4]bicyclic ring system has been demonstrated.[15] The methodology is especially useful when a specific stereochemistry is required at the spirocenter since thermodynamically less stable isomers can also be obtained. Although we are conscious that the conclusions obtained from this simple model cannot be fully extrapolated to the natural products,[16] it is interesting to note that the greatest acid-catalyzed reactivity corresponds to a compound with the natural stereochemistry.

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Supporting Information Available: Experimental procedures and characterization for all compounds. An X-ray crystallographic file (CIF) for compounds **15** and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The diol dissolved in $CHCl_3$ was treated with an undetermined catalytic amount of HCl (some gas taken with a Pasteur pipet from the headspace of a concentrated HCl bottle).

(14) Molecular mechanics calculations were performed using the AMBER* all-atom force field and the GB/SA solvation model for $CHCl_3$ as implemented in version 7.0 of the MacroModel and BatchMin packages.

(15) Shortly before submitting this Letter we became aware of the studies by Prof. P. L. Fuchs in the ASAP section of this journal (Lee, S.; LaCour, T. G.; Lantrip, D.; Fuchs, P. L. *Org. Lett.* **2002**, *4*, 313−316. Lee, S.; Fuchs, P. L. *Org. Lett.* **2002**, *4*, 317−318) where IHA reactions are used to prepare related dioxaspiro compounds.

(16) The 14,15-double bond and the 17α-hydroxyl group may have a strong influence on the stability of the dioxaspiro ring system.