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 cephalostatins¹ and ritterazines² 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 (2S,4R,5S,9S)-2-hydroxymethyl-2,9-dimethyl-1,6-dioxaspiro[4.4]nonan-4-ol substructure (see, for example, cephalostatin 1).

Their unique structure and biological activity have made them an important synthetic target. The syntheses of several...
of these natural products and analogues have been achieved, but despite efforts by several research groups, the mechanism of action of these compounds remains unknown.

Taking into account the SAR correlation of cephalexin and OSW-1, a related cholestanol glycoside isolated from a terrestrial plant, it was hypothesized that the active intermediate might be an oxycarbamerion ion located at rings E or F and originated by opening of the dioxaepipiperazine. 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 dioxaepipiper[4.4]nonane system, may also influence the activity of cephalexins.

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 alkyox radicals. In previous papers from this laboratory, we have demonstrated the utility of IHA reactions in the synthesis of dioxaepipiper[4.4]nonane ring systems in the carbohydrate field.

The synthesis starts with 3-methoxy-2-oxotigogenin (2) (Scheme 1) prepared using a previously described procedure by oxidation of 3-methoxytigogenin (1) with NaNO2/BF3, Et2O. 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 (23R) could be obtained in moderate yield. The reduction of 2 with NaBH4 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 stereo-selective opening reaction of the tigogenin dioxaepipiper[4.4]decane system present in 3 was accomplished with Ph3SiH/TiCl4 to give diol 5 in 67% yield.11

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 TBOSOTf (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 dioxaepipiperazines 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 1H and 13C 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
from the 22S-diol 19 toward the more stable 22R-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 (ΔE_{14,19} 5 kcal/ mol; ΔE_{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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(22S,23R,25S)-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 22R-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 25R series the equilibrium is also strongly displaced.

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

10

\[ \text{10} \] a

11

\[ \text{11} \] c

12 \[ \text{12} \] R¹ = \text{BuMe}_2\text{Si}, R² = \text{Ac} \rightarrow \text{13} R¹ = \text{BuMe}_2\text{Si}, R² = \text{Ac} \rightarrow \text{14} R¹ = \text{H}, R² = \text{H} \rightarrow \text{15} R¹ = \text{H}, R² = \text{H} \rightarrow \text{16}

13 \[ \text{13} \] R¹ = \text{BuMe}_2\text{Si}, R² = \text{Ac} \rightarrow \text{14} R¹ = \text{H}, R² = \text{H}

14 \[ \text{14} \] R¹ = \text{H}, R² = \text{Ac} \rightarrow \text{15} R¹ = \text{H}, R² = \text{H}

15 \[ \text{15} \] R¹ = \text{H}, R² = \text{H}

16

17 \[ \text{17} \] R¹ = \text{BuMe}_2\text{Si}, R² = \text{Ac}

18 \[ \text{18} \] R¹ = \text{BuMe}_2\text{Si}, R² = \text{Ac}

19 \[ \text{19} \] R¹ = \text{H}, R² = \text{H}

20 \[ \text{20} \] R¹ = \text{H}, R² = \text{H}

\[ \text{21} \]

\[ \text{14} \] The diol dissolved in CHCl₃ was treated with an undetermined catalytic amount of HCl (some gas taken with a Pasteur pipet from the headspace of a concentrated HCl bottle).

(12) The ratio 25R:22R of diols 15:20 in the headspace was determined by MS.

(13) See Experimental. Both diols 15 and 20 from the 25R series were obtained in a similar amount to those of the 22R isomer.

(14) Molecular mechanics calculations were performed using the AMBER*- all-atom force field and the GB/SA solvation model for CHCl₃ as implemented in version 7.0 of the MacroModel and BatchMin packages.


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

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