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Hydrogen atom transfer methodology for the synthesis of C-22, C-23, and C-25 stereoisomers of cephalostatin north 1 side chain from spirostan sapogenins

Carmen Betancor,[b] Raimundo Freire,[a] Inés Pérez-Martín,[a] Thierry Prangé[c] and Ernesto Suárez[a,*]

[a]*Instituto de Productos Naturales y Agrobiología del C.S.I.C., Carretera de La Esperanza 3, 38206 La Laguna, Tenerife, Spain*
[b]*Departamento de Química Orgánica, Universidad de La Laguna, Tenerife, Spain*
[c]*LURE, Université Paris-Sud, Paris, 91405 Orsay Cedex, France*

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Abstract—A simple synthesis of all eight C-22, C-23, and C-25 diastereoisomers of the cephalostatin north 1 side chain has been accomplished from (25*R*)-5α-spirostan-3β-ol (tigogenin). The synthesis involves selective hydroxylations at C-23 and C-25 and reductive opening of the 1,6-dioxaspiro[4.5]decane spirostan system to give a conveniently protected 5α-furostan-3β,23,25,26-tetrol. The construction of the required 1,6-dioxaspiro[4.4]nonane system entailed an intramolecular hydrogen abstraction reaction promoted by the C-25 alkoxyl radical as the key step. Acid-catalyzed isomerization of the spiroketal unit suggested that 22*R* isomers are the thermodynamic products while the 22*S* isomers are the result of kinetic control. The acid-catalyzed equilibrium between 1,6-dioxaspiro[4.4]nonane and 1,6-dioxaspiro[4.5]decane systems was also studied. In the 1,6-dioxaspiro[4.4]nonane units, the observed $^{3}J_{23,24}$ coupling constants suggest that the five-membered puckered ring-F undergoes substantial conformational changes on going from 22*S* to 22*R* isomers.

1. Introduction

Cephalostatins[1] and the structurally related ritterazines[2] comprise a group of secondary metabolites isolated from marine invertebrates (*Cephalodiscus gilchristi* and *Ritterella tokioka*, respectively) which have attracted considerable attention from synthetic organic chemists and pharmacologists due to their complex structures and significant biological properties.[3] They are alkaloids constituted by two steroidal units linked through a pyrazine ring involving the C2-C3 position of each monomeric unit and are among the most potent cytotoxins ever isolated from a natural source. In most of these substances the steroidal eight-carbon side chain has been transformed into a 1,6-dioxaspiro [4.4]nonane system. In particular, a polyoxygenated (2*S*,4*R*,5*S*,9*S*)-2-hydroxymethyl-2,9-dimethyl-1,6-dioxaspiro [4.4]nonan-4-ol substructure is found in the side chain of the north unit in many cephalostatins (17 out of 19), and the majority of ritterazines have a 2,2,9-trimethyl-1,6-dioxaspiro[4.4]nonane system on one or other side of their skeletons (Fig. 1).

The syntheses of several of these natural products and analogues have been achieved[4] and during these studies very interesting methodologies have been brought to light.[5] Nevertheless, despite efforts by several research groups, the mechanism of biological action remains unknown.[6] The structure-activity relationship between cephalostatins and OSW-1 (Fig. 1), a related cholestane glycoside isolated from a terrestrial plant (*Ornithogalum saundersiae*),[7] supports the hypothesis that the bioactive intermediate might be an oxocarbenium ion located at rings E or F and originated by opening the dioxaspiro grouping.[6,7b,8] We can deduce from this that the stereochemistries at C-22, C-23, and C-25, which doubtless have a strong influence on the conformation and 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 eight possible isomers of this system by modification of the steroidal side chain of a commercially available spirostan sapogenin,[9] the key step being the formation of the spiroketal system by an intramolecular hydrogen abstraction reaction (IHA) promoted by alkoxyl radicals.[10] 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.[11] From this previous

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* Corresponding author. Tel.: +34 922 251004; fax: +34 922 260135; e-mail: esuarez@ipna.csic.es

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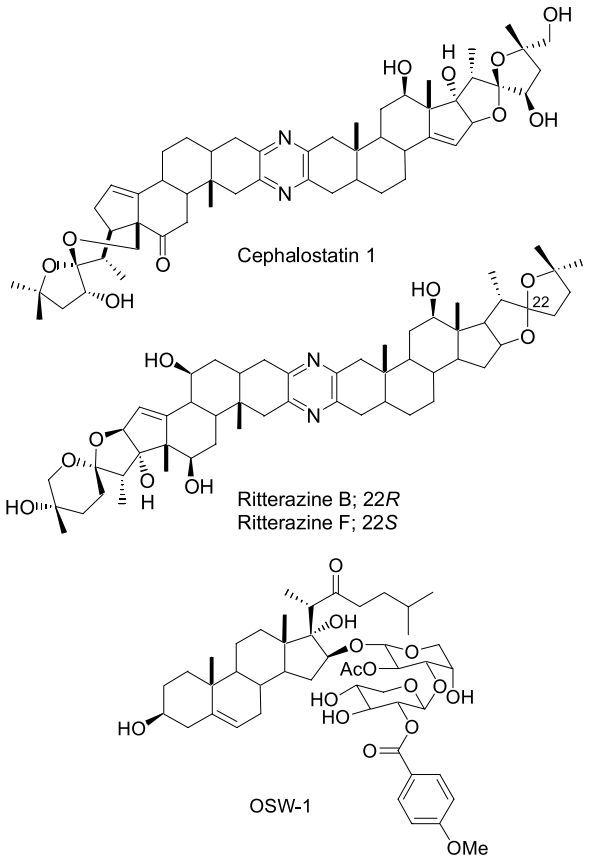
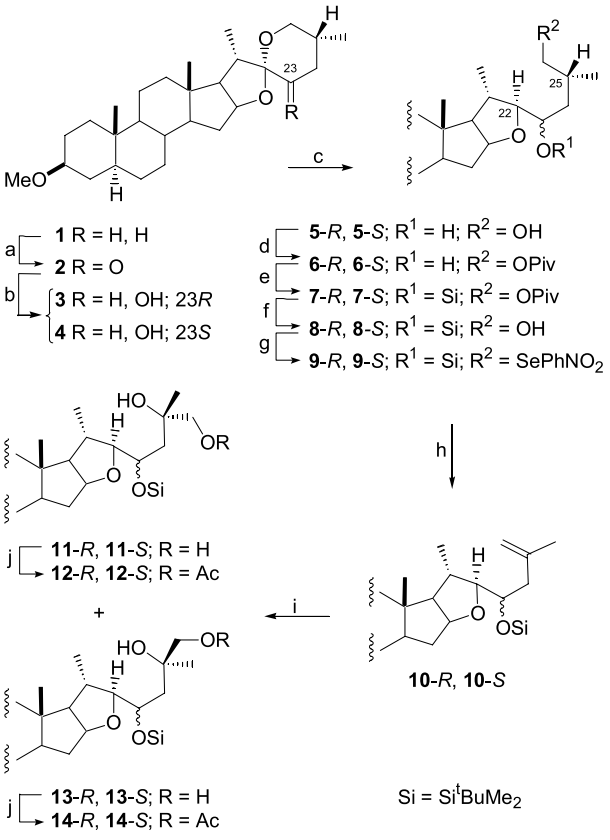


Figure 1. Examples of representative cephalostatins and reitterazines.



Scheme 1. Reagents and conditions: (a) $NaNO_2$, $BF_3{\cdot}Et_2O$, AcOH, rt, 1 h, 68%; (b) $NaBH_4$, EtOH, rt, 1 h, 91% (**3**/**4** ratio 5:95) or L-selectride, THF, −20 °C, 1.5 h, 72% (**3**/**4** ratio 63:37); (c) Ph_2SiH_2, $TiCl_4$, CH_2Cl_2, −20 °C; (d) pivaloyl chloride, Py, CH_2Cl_2, rt, **6**-*R* 95%, **6**-*S* 97%; (e) ^{t}BuMe$_2$SiOTf, CH_2Cl_2, Et_3N, rt, **7**-*R* 81%, **7**-*S* 98%; (f) KOH, MeOH, rt, **8**-*R* 92%, **8**-*S* 91%; (g) *o*-NO_2PhSeCN, *n*-Bu_3P, THF, rt, **9**-*R* 99%, **9**-*S* 97%; (h) H_2O_2, THF, rt, **10**-*R* 92%, **10**-*S* 82%; (i) OsO_4, Py, CH_2Cl_2, rt; (j) Ac_2O, Py, rt. [For yields of the (i) and (j) reactions, see supplementary data section]. The (*R*,*S*) designs the stereochemistry at C-23.

experience we were confident that both spiroketal isomers could be obtained using this methodology. This is synthetically important because in most of the ritterazines both stereoisomers at the spiroketal center were obtained from the natural source.[12]

2. Results and discussion

The synthesis began with 3-methoxy-23-oxotigogenin (**2**) (Scheme 1) prepared by using a previously described procedure via oxidation of 3-methoxy-tigogenin (**1**) with $NaNO_2/BF_3{\cdot}Et_2O$.[13] The reduction of **2** with L-selectride furnished 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 alcohol **4** (23*S*) with the non-natural stereochemistry (91%, 19:1).

The two C-23 diastereoisomers **3** and **4** were taken through the following steps of the synthesis separately (Scheme 1). The tigogenin dioxaespiro[4.5]decane system present in **3** was regio- and stereoselectively reduced with Ph_2SiH_2/$TiCl_4$ to give the diol **5**-*R*.[14] Conversion of **5**-*R* to the monoprotected secondary alcohol **8**-*R* was accomplished by a three-step protection-deprotection sequence involving formation of the primary pivalate **6**-*R*, silylation of the 23-alcohol with TBDMSOTf, and hydrolysis of pivalate **7**-*R* with KOH in methanol. Nitrophenylselenenylation of the primary alcohol in **8**-*R* followed by oxidative elimination furnished alkene **10**-*R*.[15] In a series of reactions identical to those described (Scheme 1), the 23*S* isomer **4** was converted into **10**-*S* via **5**-*S*, **6**-*S*, **7**-*S*, **8**-*S*, and **9**-*S*. Stoichiomeric osmylation of the **10**-*R* olefin afforded an inseparable mixture of diols **11**-*R* and **13**-*R* which could be separated after acetylation of the primary alcohol **12**-*R* and **14**-*R* in a 1:2 ratio (99%). In contrast, the osmylation of the **10**-*S* isomer afforded a separable mixture of diols **11**-*S* and **13**-*S* in a 2:1 ratio (98%), which were subsequently and separately acetylated to give **12**-*S* and **14**-*S*.

Initials attempts to asymmetrically dihydroxylate the 25-olefin were unsuccessful.[16] Using the Corey (1*S*,2*S*)-N^1,N^2-bis(mesitylmethyl)-1,2-diphenyl-1,2-ethanediamine reagent,[17] the **10**-*R* olefin gave the diols with similar yield and diastereomeric ratio (**11**-*R*/**13**-*R*, 1:2, 97%) compared with the uncatalyzed reaction. As both isomeric diols were required for this study the uncatalyzed osmylation reaction was preferred.

The IHA reaction was carried out by separately treating compounds **12**-*R*, **12**-*S*, **14**-*R*, and **14**-*S* with (diacetoxyiodo) benzene and iodine under irradiation with two 80 W tungsten-filament lamps at 50 °C (Scheme 2). The alcohols that possess the natural stereochemistry at C-23 (*R*) **12**-*R* and **14**-*R* gave 1,6-dioxaspiro[4.4]nonane compounds **15**