ORGANIC LETTERS

2002
Vol. 4, No. 3
313−316

Redox Refunctionalization of Steroid Spiroketals. Structure Correction of Ritterazine M†

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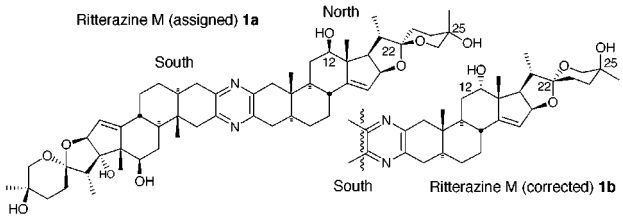
Received August 15, 2001 *(Revised Manuscript Received October 30, 2001)*

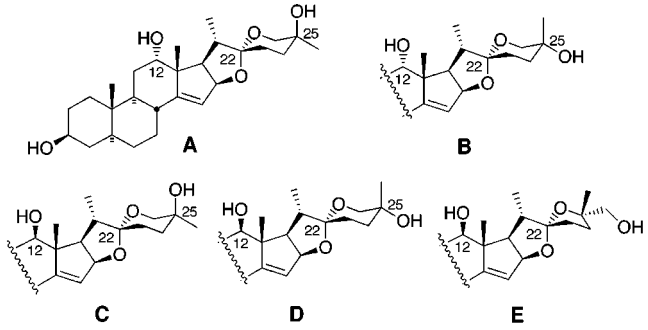
ABSTRACT



The structure of the North spiroketal moiety of ritterazine M has been corrected from 1a to 1b. This was accomplished by comparison of published spectra of the natural product with five synthetic spiroketal−alcohols. Synthesis of these models was efficiently accomplished by reductive cleavage of the spiroketal and *Sharpless asymmetric dihydroxylation of an isopentyl, methyl 1,1-disubstituted olefin*, followed by Suarez iodine[III] oxidative spirocyclization of monoprotected 1°,3° 1,2 diols.

In conjunction with our program to synthesize trisdecacyclic pyrazine anticancer agents related to the cephalostatins and ritterazines, we have developed an extensive computer database that correlates structure and bioactivity.[1] In applying this activity model to the previously reported pyrazines, we noted that ritterazine M[2] deviated substantially from the activity anticipated. Since we were using this correlation to predict structures for synthesis, it was imperative to verify the structure of this key substrate. Examination of NMR data suggested the possibility of misassignment of the stereochemistry at C-12, C-22, and C-25, but we felt that synthesis of spiroketals **A**−**E** was essential for providing a sound basis for settling the structural assignment (Scheme 1).

Scheme 1



The synthesis of our target spiroketals begins with C-12 α-benzoate **5**, available in two operations in 79% overall yield from hecogenin acetate **2**, an inexpensive plant-derived spiroketal.[3] Spiroketal cleavage using silane−BF_3·OEt_2

† Cephalostatin Support Studies. 20. For 19, see: LaCour, T. G.; Guo, C.; Boyd, M. R.; Fuchs, P. L. *Org. Lett.* **2000**, *2*, 33−36.

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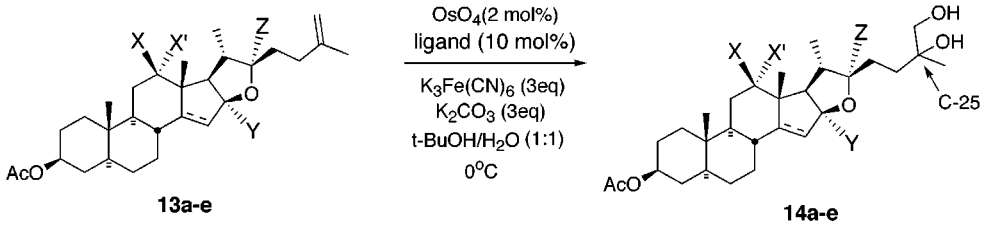
(5) For six additional stereospecific examples of this useful transformation in 5/6 and 5/5 spiroketals, see Tables 1 and 2 of the Supporting Information.

10.1021/ol0165894 CCC: $22.00
Published on Web 01/15/2002

Table 1. Asymmetric Dihydroxylation of the C-25 Olefin

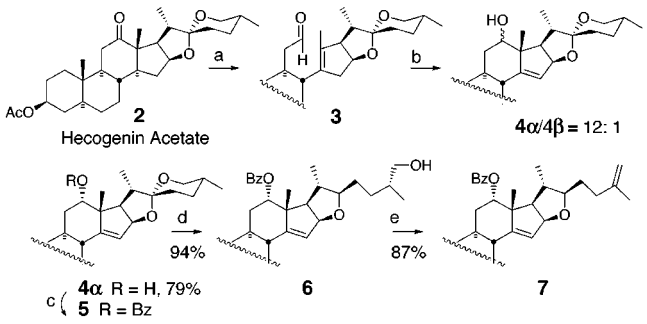


substrate	X	X′	Y	Z	C14−C15	ligand	time (h)	product	% yield	25*S*:25*R*
13a	H	OBz	H	H	Δ^{14}	$(DHQ)_2PHAL$	8	**14a**	96	5.9:1[a]
13b	H	OBz	H	H	Δ^{14}	$(DHQ)_2PYR$	28	**14b**	98	1.2:1[b]
13c	OBz	H	H	H	Δ^{14}	$(DHQ)_2PHAL$	11	**14c**	96	5.4:1[a]
13d	OBz	H	OH	H	14α-H	$(DHQ)_2PHAL$	16	**14d**	95	1:1[b]
13e	O	O	H	OMe	14α-H	$(DHQ)_2PHAL$	13	**14e**	94	1.5:1[c]

[a] Ratio based on the integration of 26-H of the radical cyclization product. [b] Ratio based on the integration of 18-Me of the diol. [c] Ratio based on the integration of 22-methoxy group.

reduction[4] stereospecifically delivers primary alcohol **6**.[5] Conversion of **6** to the primary iodide (not shown) by treatment with triphenylphosphine, iodine, and imidazole[6] followed by elimination with DBU in DMF gives olefin **7** in 87% yield (Scheme 2).

Scheme 2[a]



[a] (a) *h*ν, 25 °C, 4 d; (b) $ZnBr_2$, DCM, 25 °C, 2 h; (c) BzCl, DMAP, pyr., 25 °C 5 h; (d) $BF_3{\cdot}OEt_2$, Et_3SiH, DCM, 0 °C, 4 h; (e) i. PPh_3, I_2, imidazole, Et_2O/MeCN, 0 °C, 2 h; ii. DBU, DMF, 80 °C, 2 h.

Woodward's internal redox mechanism[7] for C-25 epimerization via C-26 to C-22 hydride transfer as adopted by Pettit[8] for the LAH-mediated reduction of steroidal spiroketals (Scheme 3) has so cemented synthetic thinking that the possibility of direct hydride addition to a C-22 oxonium ion is seldom considered.

We employ $Et_3SiH/BF_3{\cdot}OEt_2$ at 0 °C for spiroketal reductions. The reaction takes the same stereochemical course regardless of configuration or substituents at C-12/C-14 (**5a**, **5b**, **8**) or C-25/C-26 (**11a**, **11b** (Scheme 3). It is noteworthy that this mild, selective method reduces 5/5 spiroketals (1,6-dioxaspiro[4.4]nonanes), in contrast to $LAH/AlCl_3$.[8b] Only 22αD compounds were obtained with Et_3SiD, confirming that *the internal redox process was inoperative*. Ethanedithiol/$BF_3{\cdot}OEt_2$ with **8** gave exclusively 22αH-26-thioketal **10**. The latter reaction required 25 °C, suggesting that internal hydride transfer might be controlled by temperature choice. Indeed, ∼30% 22-H and ∼15% 26-D was found at 25 °C using Et_3SiD with **8**. Ireland reported a similar temperature dependence.[9] Pettit had also shown that $LAH(D)/AlCl_3$ (0

Scheme 3

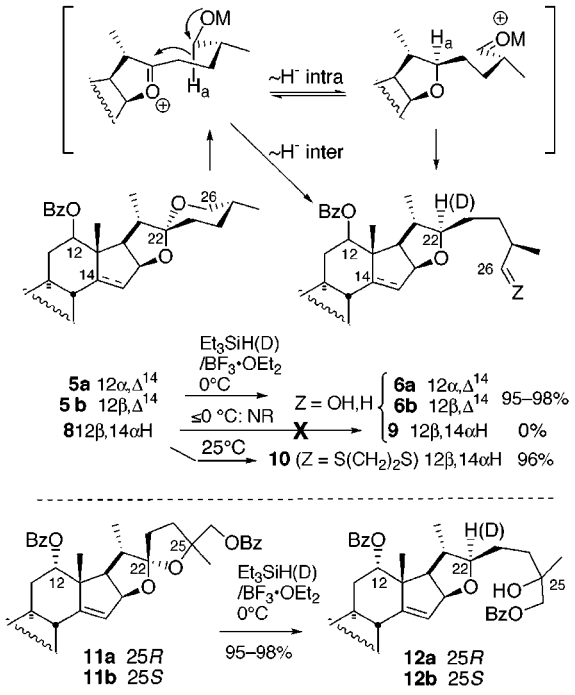


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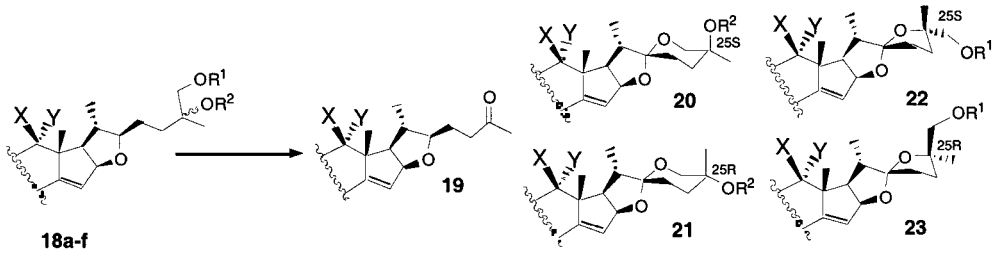
Table 2. Application of the Suarez Oxidation to the C-25,26 Diol Derivatives



substrate	X	Y	R^1	R^2	C14−C15	$PhI(OAc)_2$:I_2 (equiv)	*T* (°C)	time (h)	products[a]	% yield
18a	H	OBz	H	H	Δ^{14}	1.1:0.5	25	5	**19α**	94[b]
18b	OBz	H	TBDPS	H	14α-H	2.5:1.0	0	3	**19*β*/22*β***	42/51
18c	H	OBz	Ac	H	Δ^{14}	2.0:1.0	0	12	**22α/23α**	78/13
18d	H	OBz	H	Bz	Δ^{14}	2.0:2.0	0	8	**20α/21α**	77/14
18e	OBz	H	H	Bz	Δ^{14}	2.0:2.0	0	7	**22*β*/23*β***	78/14
18f	OBz	H	Bz	H	Δ^{14}	2.0:2.0	0	7	**20*β*/21*β***	75/15

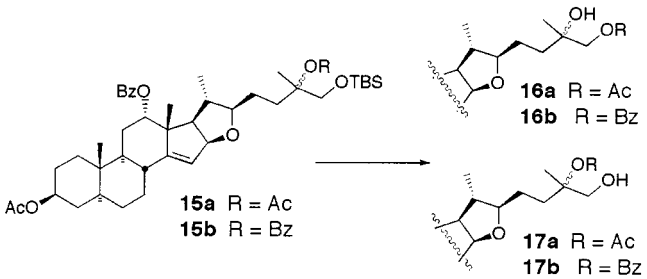
[a] The α- and *β*-compounds have the α- and *β*-C-12 benzoate, respectively. [b] Using HgO, I_2, CCl_4, 25 °C, 15 h gives a yield of **19**α of 77%.

°C, 1 h, then 40 °C, 2 h) gave 22αH(D) products with a series of steroids, ruling out internal delivery of hydride, yet $AlCl_3$ and dithiol at 25 °C gave a C-26 thioacetal.[8c]

As expected from our previous studies,[10] selective asymmetric dihydroxylation of the olefin moiety proved especially difficult. Establishment of a workable excess of the requisite 25*S* diastereomer was only obtained when employing the $(DHQ)_2PHAL$ ligand (Table 1). This effect extended to both C-12 benzoates but was only seen with the C-14,15 olefins, while sp^3 centers at C-14,15 completely eroded the reagent-based stereoselection.

Having developed a satisfactory protocol for installation of the distal C-25(*S*),26 diol moiety, we next turned to reestablishment of the spiroketals. For this transformation we adopted the hypoiodite method so successfully pioneered by Suarez. In preparation for reestablishment of the 5/6 spiroketal (1,6-dioxaspiro[4,5]decane) [VITA 143] it was necessary to protect the tertiary alcohol in order to avoid oxidative cleavage of the 1,2-diol. While silylation of the primary alcohol of the C-25(*S*)-rich diol mixture followed by acetylation of the tertiary alcohol generates **15a** in 21% overall yield, numerous fluoride and acidic attempts to deprotect silyl ether **15a** to alcohol **17a** resulted in extensive acyl migration, mainly yielding primary acetate **16a** with variable but minor amounts of the desired primary alcohol **17a** (Scheme 4). In stark contrast, silyl benzoate **15b** is

Scheme 4



readily deprotected to tertiary benzoate **17b** in 96% yield without formation of any of the acyl migration product **16b**.

Application of the Suarez oxidation[11] to the C-25,26 diol derivatives prepared in Table 1 revealed several important points (Table 2). The first of these was that diols and monosilyl ether were not appropriate substrates as they suffered significant to extensive cleavage to ketone **19** (**18a**−**b**). Primary monoacetate **17a** cyclized with high efficiency to stereospecifically provide 5/5 spiroketals, revealing the osmylation ratio of **22α/23α** to be 5.9:1 (**18c**). The monobenzoates (**18d**−**f**) proved to be the substrates of choice, each affording a high yield of the desired 5/6 spiroketals **20/21**, which were easily separated by chromatography at this stage. Global deprotection of **20**α, **21**α, **20***β*, **21***β*, and **22**α provided target spiroketals **A**, **B**, **C**, **D**, and **E** (Scheme 1), respectively.

Using a 3-D presentation of the Kishi comparison format (Figure 1),[12] it appears that the North spiroketal unit of ritterazine M bears the unusual α axial C-12 alcohol along with the more typical α C-22 oxygen configuration and C-25 axial alcohol as shown in the corrected structure **1b**. A point

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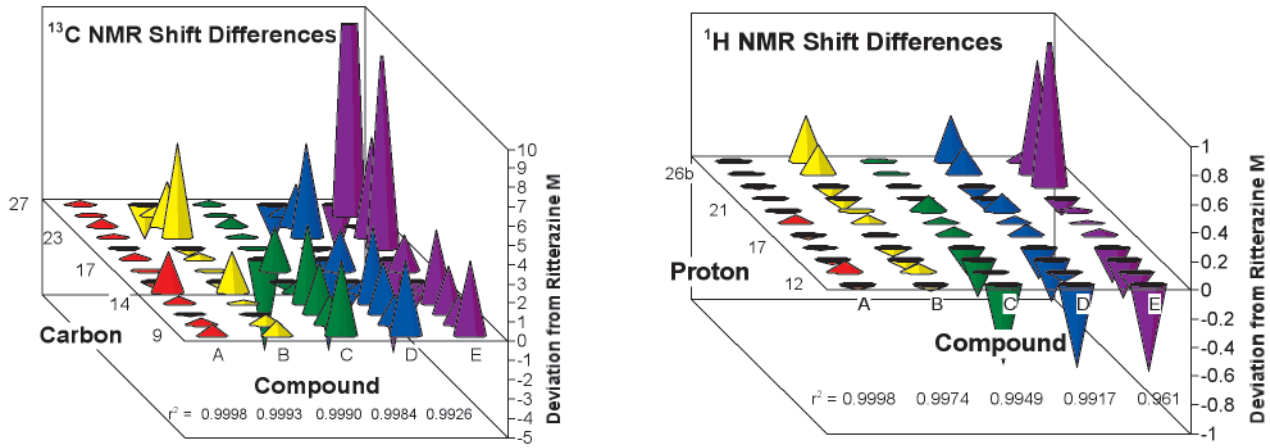

Figure 1. Differences in NMR shift values when compared to authentic ritterazine M. **A**: 12α-OH, 25*S*, 5/6 spiroketal, 3*β*-OH, Δ^{14}. **B**: 12α-OH, 25*R*, 5/6 spiroketal, 3*β*-OH, Δ^{14}. **C**: 12*β*-OH, 25*S*, 5/6 spiroketal, 3*β*-OH, Δ^{14}. **D**: 12*β*-OH, 25*R*, 5/6 spiroketal, 3*β*-OH, Δ^{14}. **E**: 12*β*-OH, 25*S*, 5/5 spiroketal, 3*β*-OH, Δ^{14}.

of concern is the deviation of the C-15 shift in compound **A**. This resulted from an inadvertent cross-assignment[2] of the olefinic C-15 and C-15′ carbons in the ^{13}C NMR of the natural product (assigned 119.0 ppm; actually 120.7 ppm which correlates better with compound **A** at 121.1 ppm). Support for the corrected assignment can be seen by comparison of the chemical shift data for the remaining family of ritterazines.[13] Additional proof of the details of the structure correction is found in the following paper.[14]

An efficient process has been established to convert hecogenin acetate to C-25 hydroxylated 5/6 or 5/5 spiroketals bearing the C-22,25 stereochemistry of the cephalostatin and ritterazine class, compounds which exhibit subnanomolar anticancer activity. Using this protocol, the structure of the North spiroketal of ritterazine M has been corrected from **1a** to **1b**.

Acknowledgment. We acknowledge Arlene Rothwell and Karl Wood for MS data and thank the National Institutes of Health (CA 60548) for financial support.

Supporting Information Available: Experimental and spectral details. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0165894

(13) See Supporting Information, p 32, ref 14.
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