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Synthesis and Structure Elucidation of a Novel Ecdysteroid, Gerardiasterone

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Abstract: The structure of a novel ecdysteroid, gerardiasterone, is elucidated as **2a** by its synthesis employing a diastereoselective dihydroxylation of the *E*-olefin **22** as a key step.

Gerardiasterone, isolated from the Mediterranean zoanthid *Gerardia savaglia*,[1] is a new ecdysteroid with a 20,22,23,25-tetrahydroxylated side chain. Although the structure determination of gerardiasterone was attempted on the basis of the NMR study, the configurations on the side chain remained still obscure, and the structure was tentatively proposed as shown in **1**.[1] In connection with our continuing work on the synthesis of physiologically active steroids with highly oxygenated side chains,[2] we are interested in the synthesis and structure determination of gerardiasterone, and report here the diastereoselective synthesis of **2a**, which is identical with gerardiasterone, thereby confirming its configurations.

Since most 20-hydroxylated ecdysteroids, such as crustecdysone and ponasterone A, possess (20*R*)-configuration,[3] we assumed the stereochemistry at the C-20 for **1** to be the same configuration as those. We first investigated the determination of stereochemistries on the side chain using model compounds **2b-5b**. The requisite 22,23-diol functionalities were constructed by employing dihydroxylation of *E*- and *Z*-olefins **11** and **12** as follows (Scheme 1). The *E*- and *Z*- side chain units **8** and **9** were prepared from the acetylenic compound **6**[4] *via* **7** by the usual method.[5] Addition of the alkenyllithiums, obtained by lithiation of **8** and **9**, to the 20-oxo steroid **10** afforded the allyl alcohols **11** and **12**, respectively.

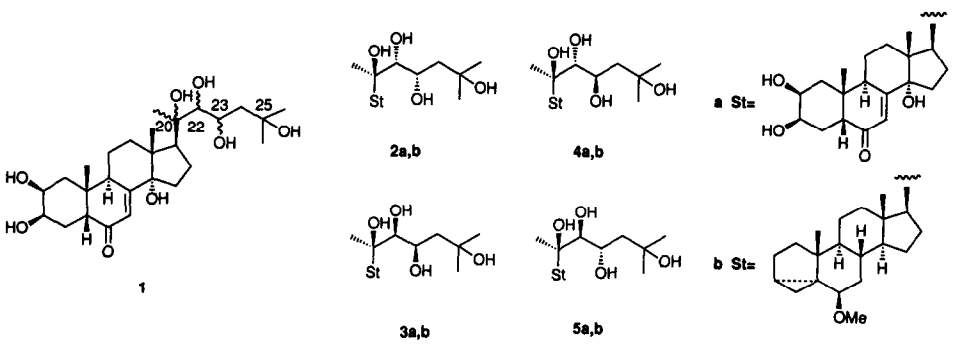
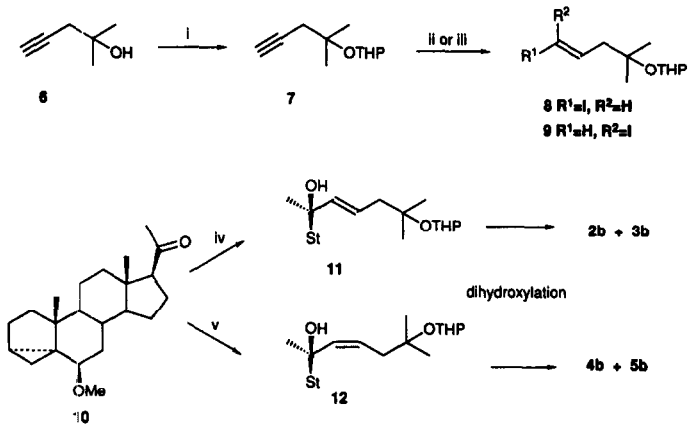


Figure 1

Dihydroxylation of **11** and **12** using stoichiometric osmium tetroxide[6] was studied under several conditions and the results are shown in Table 1, which clearly indicated that the use of chiral ligands,[7] dihydroquinine *p*-chlorobenzoate (DHQ-CLB) and dihydroquinidine *p*-chlorobenzoate (DHQD-CLB), effected the improvement of the diastereoselectivities,[8] especially in the case of the *E*-olefin **11**. Although four tetraols **2b-5b** were obtained in hand, the stereochemistries of these compounds could not be established at this stage.



Scheme 1 *Reagents and conditions:* i, DHP, *p*-TsOH, CH_2Cl_2, 85%; ii, 1) *n*-Bu_3SnH, AIBN, 95%, 2) I_2, pyridine, CH_2Cl_2, 99% (**8**); iii,1) I_2, morpholine, benzene, 80%, 2) $KO_2CN{=}NCO_2K$, AcOH, MeOH, 90% (**9**); iv, **8**, *t*-BuLi, THF, -78°C, 70%; v, **9**, *t*-BuLi, THF, -78°C, 84%

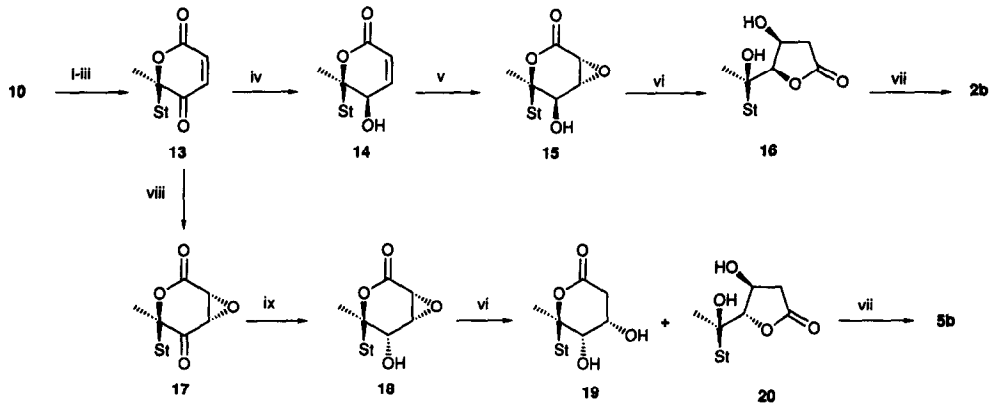
Table 1 Dihydroxylation of the olefins **11** and **12** using osmium tetroxide[a]

	dihydroxylation of **11**		dihydroxylation of **12**	
	yield (%)	ratio of products[b] **2b : 3b**	yield (%)	ratio of products[b] **4b : 5b**
OsO_4 pyridine	85	76 : 24	93	54 : 46
OsO_4 DHQ-CLB	80	91 : 9	92	71 : 29
OsO_4 DHQD-CLB	87	13 : 87	84	35 : 65

[a] All reactions were run with stoichiometric osmium tetroxide (1.2 eq.). Removal of the tetrahydropyranyl group with camphorsulphonic acid provided the tetraols **2b-5b**.
[b] Ratios were determined by ^1H NMR spectral analyses.

We, therefore, carried out an alternative synthesis of two diasteroisomers **2b** and **5b** in order to confirm the structures **2b-5b** as follows (Scheme 2). Enone **13**, prepared from **10** according to our previous results,[2a] was reduced with sodium borohydride in the presence of cerium(III) chloride to give the allyl alcohol **14**, whose epoxidation with sodium hypochlorite[9] afforded the epoxide **15** as a sole product. The observed stereoselectivities in the reduction and epoxidation reactions could be explained by assuming that the reactions occurred preferentially from the less hindered sides of the molecules. Treatment of **15** with sodium phenylseleno(triisopropoxy)borate[10] brought about regioselective ring opening of the epoxide followed by spontaneous recyclization of the corresponding β,γ-dihydroxy-δ-lactone to furnish the γ-lactone **16**, which was further treated with methylmagnesium bromide to afford the desired tetraol **2b**. Compound **13** was similarly transformed into **5b** by epoxidation with alkaline hydrogen peroxide, sodium borohydride reduction of the ketone **17**, reductive cleavage of the epoxide **18** and methylation of the lactones **19** and **20**. Since the tetraols **2b-5b** were produced by the dihydroxylation of **11** and **12**, their structures were confirmed as Fig. 1. The ^1H NMR spectral data of the model compounds **2b** and **3b** with 22,23-*syn* diol functionality are close to those of

gerardiasterone,[1] whereas the 22,23-*anti* isomers **4b** and **5b** are quite different(Table 2). Thus, we tentatively assigned gerardiasterone as **2a** or **3a** not **4a** or **5a**.



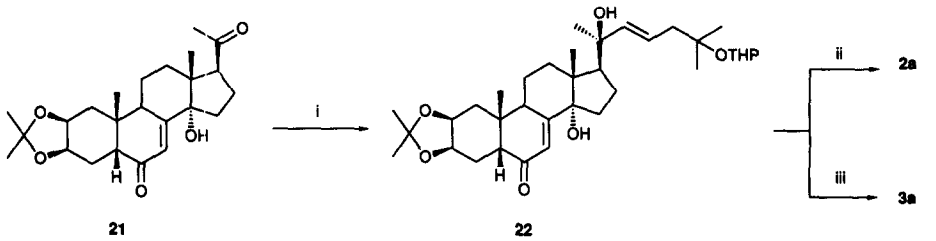
Scheme 2 *Reagents and conditions:* i, 2-lithiofuran, THF, -78°C; ii, NBS, aq. THF; iii, PCC, NaOAc, CH_2Cl_2, 83% from **10**; iv, $NaBH_4$, $CeCl_3$, MeOH, 97%; v, NaOCl, pyridine, 62%; vi, $(PhSe)_2$, $NaBH_4$, AcOH, *i*PrOH, 63% (**16**), 53% (**19** : **20** = 1 : 1); vii, MeMgBr, THF, 25% (**2b**), 22% (**5b**); viii, 35% H_2O_2, 0.5M NaOH, THF, EtOH, 80%; ix, $NaBH_4$, THF, -70°C, 87%

Table 2 ^{1}H NMR spectral data of gerardiasterone **1** and the tetraols **2b-5b**[a]

	21-H_3	26-, 27-H_3		22-H	23-H
1[b]	1.77	1.44	1.47	3.75 (br s)	4.85 (br d, *J*= 9.7 Hz)
2b	1.72	1.51	1.58	3.71 (br s)	4.78 (br d, *J*= 8.6 Hz)
3b	1.81	1.41	1.48	3.67 (br s)	5.01 (br d, *J*= 9.8 Hz)
4b	1.75	1.48	1.57	3.88 (d, *J* = 6.7 Hz)	4.60 (d t, *J*= 6.7 and 1.7 Hz)
5b	1.81	1.42	1.48	3.69 (t, *J* = 7.9 Hz)	4.67 (t, *J*= 7.9 Hz)

[a] ^{1}H NMR spestra were obtained for solutions in C_5D_5N. [b] See ref. 1.

With the results in mind, we embarked on the diastereoselective synthesis of **2a** and **3a** as follows (Scheme 3). Addition of the alkenyllithium, prepared from **8**, to the ketone **21**[11] furnished the *E*-olefin **22**, whose dihydroxylation[12] with a chiral ligand (either DHQ-CLB or DHQD-CLB) followed by removal of all the protecting groups afforded the ecdysteroids **2a** (65% from **22**) as a colorless amorphous solid, m.p. 140-143°C(lit.[1] m.p. 143-146°C); $[\alpha]_D^{26}$ +57.8 (c 0.1, MeOH){lit.[1] $[\alpha]_D^{22}$ +52.3 (c 0.35, MeOH)}, and **3a** (54% from **22**) as a colorless amorphous solid, m.p. 147-148°C; $[\alpha]_D^{26}$ +73.3 (c 0.06, MeOH). The ^{1}H NMR spectral data of **2a** are identical with those of gerardiasterone, whereas those of **3a**[13] are different, especially the resonances for 18-H_3, 21-H_3 and 23-H. Thus, the configurations of gerardiasterone is determined to be **2a**.



Scheme 3 *Reagents and conditions:* i, 8, *t*-BuLi, -78℃, 0.5 h, 70%; ii, 1) OsO_4, DHQ-CLB, *t*-BuOH, then $NaHSO_3$, pyridine, H_2O; 2) CSA, MeOH, 65% from **22**: iii, 1) OsO_4, DHQD-CLB, *t*-BuOH, then $NaHSO_3$, pyridine, H_2O; 2) CSA, MeOH, 54% from **22**

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Refereces and Notes

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2. (a) Kametani, T.; Tsubuki, M.; Furuyama, H.; Honda, T. *J.Chem.Soc., Chem.Commun.* **1984**, 375-376. (b) Kametani, T.; Tsubuki, M.; Higurashi, K.; Honda, T. *J.Org.Chem.* **1986**, *51*, 2932-2939. (c) Kametani, T.; Katoh, T.; Tsubuki, M.; Honda, T. *J.Am.Chem.Soc.* **1986**, *108*, 7055-7060. (d) Kametani, T.; Keino, K.; Kigawa, M.; Tsubuki, M.; Honda, T.*Tetrahedron Lett.* **1989**, *30*, 3141-3142. (e) Honda, T.; Keino, K.; Tsubuki, M. *J.Chem.Soc.,Chem.Commun.* **1990**, 650-651. (f) Tsubuki, M.; Kanai, K.; Kakinuma, N.; Honda, T. *J. Org.Chem.* **1992**, *57*, 2930-2939. (g) Tsubuki, M.; Keino, K.; Honda, T. *J.Chem.Soc.,Perkin Trans.1* **1992**, 2643-2649.
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6. Dihydroxylation of the olefins **11** and **12** using a catalytic amount of osmium tetroxide and an appropriate oxidant was sluggish.
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11. Mori, H.; Shibata, K. *Chem.Pharm.Bull.* **1969**, *17*, 1970-1973.
12. The ratios of the dihydroxylation of the *E*-olefin **22** were as follows. OsO4 pyridine, **2a** : **3a**=79 :21; OsO4 DHQ-CLB, **2a** : **3a**=95 : 5; OsO4 DHQD-CLB, **2a** : **3a**=21 : 79.
13. **3a**: ^{1}H NMR (270 MHz, C_5D_5N): 1.08(3H, s, 19-Me), 1.20(3H, s, 18-Me), 1.41 and 1.48(each 3H, each s, 26- and 27-Me2), 1.85(3H, s, 21-Me), 3.72(1H, br s, w/2=4 Hz, 22-CH), 5.05(1H, br d, J=9.8 Hz, 23-CH).

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