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SYNTHETIC STUDIES RELATED TO LATRUNCULIN. SYNTHESIS OF TETRAHYDROPYRANYLTHIAZOLIDIN-2-ONE SYSTEMS

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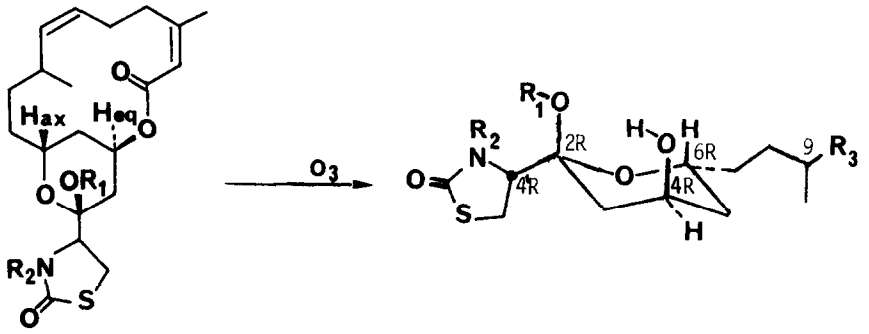
ABSTRACT

Several 4-tetrahydropyranyl-thiazolidin-2-one systems have been synthesized either by degradation of latrunculin -B (1a) or synthetically from L-cysteine. The NMR study of the compounds revealed that whereas the degradation compounds of 1 exist in a single cyclic hemiketal form, the other, synthetic, compounds exist in equilibrium mixtures.

The interesting biological activity of the fish toxins the latrunculins[1] on the cytoskeletal protein-actin[2] intrigued a structure-activity relationship study. In frame of this investigation we have prepared a series of tetrahydropyranyl(THP)-thiazolidin-2-one derivatives by either degradation of latrunculin-B (1a) or synthetically from L-cystein.

Reductive ozonolysis of the macrolide of 1b afforded compound 3a[3] which upon acidic deketalization gave compound 2 (Scheme 1).



1a $R_1=R_2=H$
1b $R_1=Me$ $R_2=H$
1c $R_1=Me$ $R_2=Bn$

2 $R_1=R_2=H$ $R_3=CH_2OH$
3a $R_1=Me$ $R_2=H$ $R_3=CH_2OH$
3b $R_1=Me$ $R_2=H$ $R_3=CHO$
10 $R_1=Me$ $R_2=Bn$ $R_3=CH_2OH$

Scheme 1

The ozonlysis furnished also compound 3b[4] possessing the 6-carboxaldehyde side chain, which was earlier suggested as a possible synthon for the latrunculins[1]. As with latrunculin-B itself, the THP ring in 2 & 3 maintains the conformation in which both the 2-thiazolidinone and the 6-side chain are equatorial and the 2-OR and 4-OH groups axial[5], most likely due to: a. the larger THP-substituents prefering the equatorial positions b. the anomeric effect of the 2-OR group[6] and c. the hydrogen bond between the axial 2-OH and 4-OR groups[5]. The latter factor may also further contribute to the stabilization of the THP-ring over the open hydroxy ketone[7]. The open form is observed in ca.5-10% in several THP derivatives as e.g. 6c, Scheme 2.

The synthesis of the model bicyclic heterocycles started with compounds 4 or 5 (Scheme 2). Compound 4 was obtained from the Pd(0) catalysed coupling of TBDMS-oxybutynyl tributylstannane with the acyl chloride of N-benzyl-2-oxo-thiazolidine-4-carboxylic acid[8].

Hydrogenation of 5 over Lindlar catalyst led to the cis α,β -enone 6; a 1:1 mixture of the 2R,4'R and 2S,4'R epimers (6a,6b), accompanied by the open enone 6c (5%)[9]. Hydrogenation of 5 over $Pd/BaSO_4$ in pyridine on the other hand, furnished the trans α,β-enone 7[10] which could also be easily obtained from 6 by basic equlibration.

Michael addition of MeOH, in the presence of K_2CO_3, to 6 or 7[11] followed by ketalization of the lactol by addition of BF_3-etherate to the MeOH solution, gave a mixture of mainly two, out of four possible, 2,4-dimethoxy derivatives, compounds 8 & 9 (55% from 6).[12]

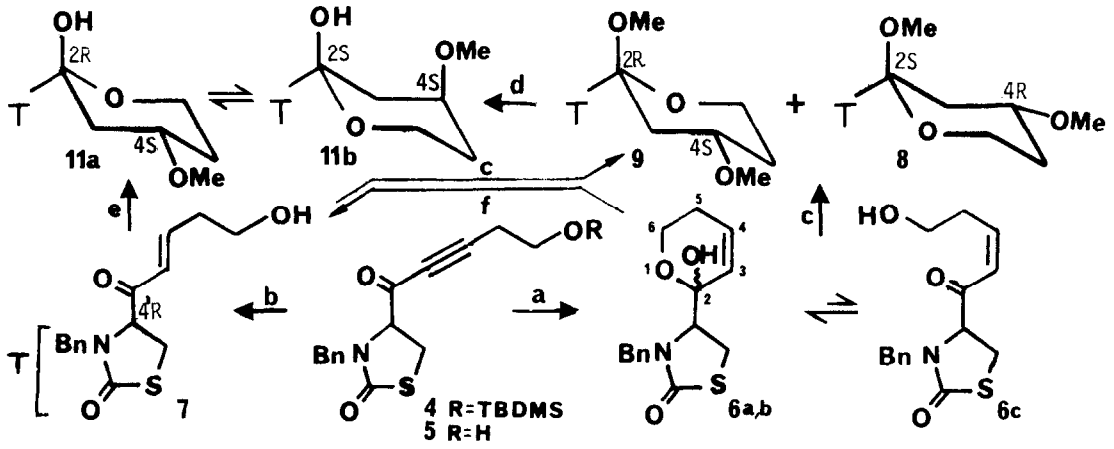
In each of these compounds the 2-OMe is axial as confirmed by an NOE experiment[13] and the 4-OMe group equatorial[12].

Compounds 8 & 9 which were separated by HPLC[14] have therefore to be of the 2S,4R,4'R and 2R,4S,4'R configuration respectively. Tentatively, based on the $\Delta\delta_{PhCH}$ values of 8 & 9 which were compared to two latrunculin derivatives, compound 1c[15] and 10[16], as well as on δ_C-value comparisons, we suggest that the main isomer, 9, is of the 2R configuration as in 1c and 10.

Upon acidic treatment each one of compounds 8 & 9 afforded the corresponding lactol; slower moving spots on the TLC plate. In case of compound 9, the acidic deketalization-product exists as a 40:60 mixture of the two possible 2,4-isomers, that is, the 2R,4S and 2S,4S diastereomers 11a & 11b respectively (Scheme 2). Whereas the equatorial 4-OMe group in 11a avoids the 1,3-diaxial interaction between the 2-hydroxy and 4-methoxy groups, the latter interaction is compensated in 11b by a strong hydrogen bond between the 2-OH and 4-OMe groups (δ_H 5.73 sharp singlet).[17]

Methanol addition to compound 7, without ketalization, led to a mixture of the 2-OH, 4-OMe derivatives in which one of the two isomers possessing the 2ax-OH and 4ax-OMe groups predominates.

This report demonstrates the synthesis of 2,4,6-trisubstituted THP-rings as well as various 2,4-disubstituted ones. The developed synthesis of the latter compounds is presently utilized for the preparation of THP derivatives possessing at C-2 the latrunculin substitution pattern and at C-4 various alcohol derivatives for biological evaluation.



Scheme 2

a. H_2 Lindlar catalyst b. H_2 $Pd/BaSO_4$ pyridine c. 1. MeOH, K_2CO_3 anhy. 2. BF_3 etherate d. SiO_2, H^+ e. MeOH, K_2CO_3 f. MeOH, pyridine.

References

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3. The $NaBH_4$ solution is basic enough to induce hydrolysis of the initially obtained $ROCOCH_2OH$ ester at C-4. Compound 2; m/z (CI) 288(MH^+-H_2O); δ_H 0.83d (J=6.6; CH_3), 3.70m(H-6), 3.98m(H-4) 3.38d(H-10), 3.73dd(H-4'). Compound 3a; m/z(CI)288 (MH^+-MeOH,100%), 270(40%); δ_H 0.95d(J=6.6;CH_3), 3.30s(OMe), 3.32dd (J=11.7,6;H-5'), 3.40dd(J=11.5,9;H-5'). 4.08dd(J=9,6;H-4'), 3.50d(J=5.7;H-10), 4.15quin(J=3.1;H-4) 3.90m(H-6) and 5.87(NH).

4. Compound 3b was obtained either together with 3a or alone by reduction of the ozonide with Zn/HOAc; m/z (CI) 318(MH^+,4.5%), 286 (MH^+-MeOH,100); δ_H 9.63d (J=1.7, CHO), 1.12d(J=7.2;Me), 3.90m(H-6) and 4.18quin (J=3;H-4).

5. The concentration independence of the OH NMR signal (at ca.5.5ppm) points clearly to a strong intramolecular hydrogen bond between the 2 & 4 diaxial groups.

6. An anomeric effect of ca. 1.3-1.8 kcal/mole, depending on the solvent, is suggested. C.B Anderson and D.T. Sepp Tetrahedron 24, 1707 (1968)

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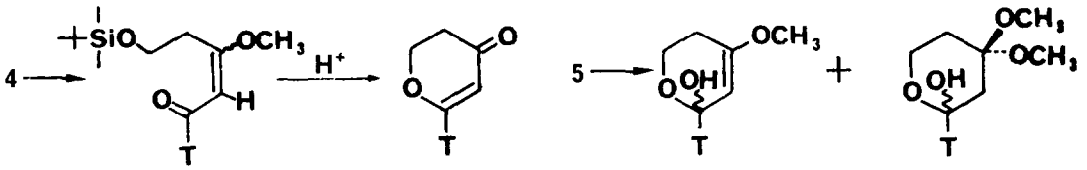
9. Compound 6; m/z (CI) 292(MH^+,2.5%), 273(2.5), 192(100), 99(C_5H_7O,6); δ_H 4.535d, 4.408d, 5.190d, 5.060d(J=14.7;Bn), 6.185bdd & 6.204bdd(J=10.2,1;H-3), 5.876ddd &

6.009ddd(J=10.2,2.7,1.2;H-4), 6.486dt(J=11.5,7.5) and 6.270dt(J=11.5,1.3)H-3 & 4 of 6c, 3.93m(H-4'), 4.16dd(H-4' of 6c);δ_C 96.6s,95.7s(C-2),63.8d,63.6d(C-4'), 65.5d(C-4' of 6c), 150.2d,123.90d(C-3&4 of 6c).

10. Compound 7; m/z (EI) 291(M^+,1.2), 273(2.5),192(100); δ_H 7.00dt(J=15.7,7.5;H-4), (the No's are according to 6a), 6.25d(J=15.7; H-3), 4.230dd(J=9.3,4.4;H-4'), 5.136d & 3.827d(J=14.9;Bn).

11. Interesting are also the Michael additions to compounds 4 or 5 affording:



12. Compound 8; m/z(CI) 338(MH^+,13%); δ_H 2.92s(OMe),3.30s(OMe), 3.55tt(J=11.5,4.8; H-4ax),3.88dd(J=9,4;H-4'), 4.24d & 5.21d(J=15.8;PhC$\underline{H}_2$); Compound 9; m/z(CI) 338(MH^+),306(MH^+-MeOH,100%); δ_H 3.02s(OMe), 3.28s(OMe),3.51dddd(J=11.1,11.5, 4.6,4; H-4ax), 3.78dd(J=9.2,2.7;H-4'), 4.31d & 4.98d(J=14.6;PhC$\underline{H}_2$); δ_C 172.7 (C-2'), 103(C-2), 60.1(C-4'), 59.5(OMe),47.4(OMe) & 48.0(Ph$\underline{C}H_2$).

13. Compound 8 exhibited NOE's between 2ax-OMe and H-4' & H-6ax and compound 9 between 2ax-OMe and H-6ax, H-4' & PhC$\underline{H}_2$.

14. Compounds 8 & 9 were obtained in 55% from 6 in a ratio of ca. 1:3 respectively and were separated on a Si-60 HPLC column eluted with 12% EtOAC; 88% cyclohexane.

15. Compound 1c was obtained from 1b by addition of 1 equivalent of NaH followed by benzylbromides; m/z(CI) 500(MH^+, 0.7%), 468(M-OMe,100%), 450(56%), δ_H 5.13d & 4.40d (J=14.6, PhC$\underline{H}_2$), 5.18bs(H-13), 4.28bt(J=10.5,H-11), 3.80dd(J=9.1,2.9,H-16) 3.12s(OCH_3).

16. Compound 10 was obtained by ozonolysis of 1c followed by $NaBH_4$ reduction; m/z (CI) 378(MH^+-MeOH) δ_H 1.15d(J=6.7,Me),3.03s (OMe),3.46d(H_2-10),3.80m(H-6), 4.15quin(J=3,H-4),4.30dd & 5.05d(J=14.6,PHC$\underline{H}_2$);δ_C 102(C-2),59.4(C-4') & 48.1 (Ph$\underline{C}H_2$); $\Delta\delta_{PhC\underline{H}_2}$ for compounds: 10 0.75; 1c 0.73; 9 0.67 and 8 0.97. The biological activity of compound 10 will be reported elsewhere.

17. Deketalization of 9 was achieved by stirring of its solution in CH_2Cl_2 in the presence of acidic silica; Compound 11; δ_H 3.36s & 3.40s(4-OMe), 3.87tt(H-4eq), 3.50m(H-4ax), 5.73s (O$\underline{H}$),4.54 & 5.14(J=14.5) and 4.37 & 5.13(J=14.8) PhC$\underline{H}_2$. The ratio of 11a/11b changes with solvent.

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