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THE SYNTHESIS OF (±)-CAVERNOSINE

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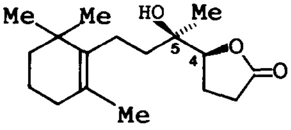
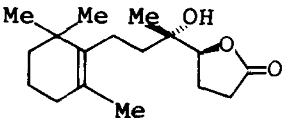
Summary: The title compound and its epimer were synthesized in three and two steps from dihydro-β-ionone and 2-trimethylsiloxyfuran in 38 and 63% overall yields respectively. Their relative configurations were confirmed by X-ray of an intermediate.

Cavernosine (1) is a novel ichthyotoxic γ-lactone of terpenoid origin which was recently isolated from the marine sponge *Fasciospongia cavernosa*.[1] Inspection of the proposed structure 1 suggests that its synthesis could be conveniently achieved by applying our diastereoselective δ-hydroxy-γ-lactone forming method.[2] The critical connection could be effected by the directed aldol condensation of dihydro-β-ionone (2)[3] with 2-trimethylsiloxyfuran (3). By analogy with the behavior of 3 towards aldehydes,[2] the diastereotopic approaches of 3 to dihydro-β-ionone (2) should be amenable to divergence by the proper choice of conditions. The result will be the formation of the threo and erythro butenolides (4 and 5) which, on hydrolysis and reduction, would yield the desired natural product 1 as well as epicavernosine 8.



1 (erythro)



8 (threo)

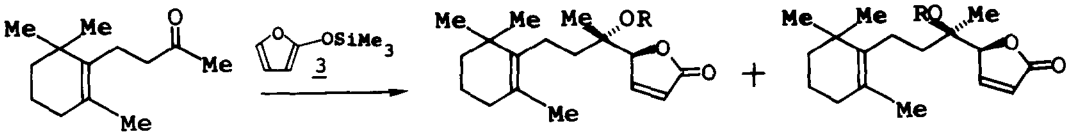
In practice, the result with Lewis acids was just like the aldehyde case. They efficiently catalyzed the condensation of 2 and 3 giving alcohols 6 and 7 with pronounced kinetic threo diastereoselectivity (Table). Yields and stereoratios were preparatively useful for the conventional catalysts (entries 1, 2 and 4). The trityl cation performed the least well on both counts (entry 5). $TiCl_4$ gave the highest ratio (83:17) at the expense of yield owing to the presumed decomposition of 3 (entry 3). The best compromise between ratio and yield was found with triethylsilyl trifluoromethanesulfonate (TESOTf) and its homologues (entry 6).[6]

Table. Electrophile-induced Condensation of 2-Trimethylsiloxyfuran (3) with Dihydro-β-ionone (2) to give threo and erythro Butenolides (6 and 7).

Entry	Conditions[a]	Threo (6)/ erythro (7)[b]	Yield[c]
1	$SnCl_4$ (0.4 eq) -78°, 2h	70:30	63
2	$ZnBr_2$ (0.35 eq) 0°→20°, 71h	71:29	89
3	$TiCl_4$ (1.2 eq) -78°, 2h	83:17	44
4	$BF_3{\cdot}Et_2O$ (1.5 eq) -78°, 1.5h	72:28	90
5	$TrClO_4$[d] (0.1 eq) -78°→20°, 4h	64:36	70
6	TESOTf[e], (0.1 eq) -78°, 2h	80:20	94

[a] CH_2Cl_2 was used as solvent and 1.2 eq. of 3 in all instances. [b] Determined by ^1H-NMR (360 MHz). [c] The reaction mixture was quenched with aqueous 2N HCl. The resulting siloxanes 4 and 5 were desilylated to 6 and 7 by homogeneous hydrolysis with THF/2N HCl, 1 hr, at 20°.[4] Yields refer to isolated diastereomeric mixtures after chromatography on SiO_2. [d] $TrClO_4$ = trityl perchlorate.[5] [e] Trimethyl and dimethyl-t-butylsilyl triflates behaved similarly.

Again, on the basis of the aldehyde precedent, the fluoride ion-induced condensation of 3 with 2 should reverse the stereochemical outcome. In fact, dihydro-β-ionone (2), proved to be inert. Both tetra-n-butylammonium fluoride (TBAF) and CsF in THF were ineffectual.[7] Nevertheless, satisfactory erythro diastereoselectivity was obtained by equilibrating the kinetic mixture of silyl ethers 4 and 5 which were conveniently available as they survived quenching.[4] Treatment with TBAF in THF for 40 hrs at -78° to -10° followed by addition of aqueous acid and standard work-up gave alcohols 6 and 7 in which the erythro isomer 7 predominated (33:67).



2

4 R = $SiMe_3$
6 R = H
(threo)

5 R = $SiMe_3$
7 R = H
(erythro)

The threo isomer 6 was separated from the threo-dominated diastereomeric mixtures simply by crystallization (ether/hexane, -78°), whereas the erythro epimer 7, was purified by chromatography of the erythro-enriched mixture over a silica gel column (eluant: ether/hexane

9:1, R_f 6 = 0.32, R_f 7 - 0.37).[8] By these procedures, either diastereomer 6 or 7 could be produced at will from 2 in 69 and 40% yield respectively.

Although the NMR data distinguished between 6 and 7, an uncertainty exists as to which is which. The same is true of cavernosine 1 since the relative configuration at C4 and C5 was only established by NOE on a derivative.[1] Fortunately, 6 gave a suitable crystal enabling its structure to be determined by X-ray (Fig.).[9] Subsequent chemoselective reduction of the butenolides 7 and 6 with $NaBH_4/NiCl_2$ afforded the corresponding natural and epimeric racemic products 1 and 8 in 94 and 91% yields respectively.[10] Comparison of the NMR data of synthetic 1 and 8 with that of natural cavernosine confirms the erythro configuration of the latter.[8]

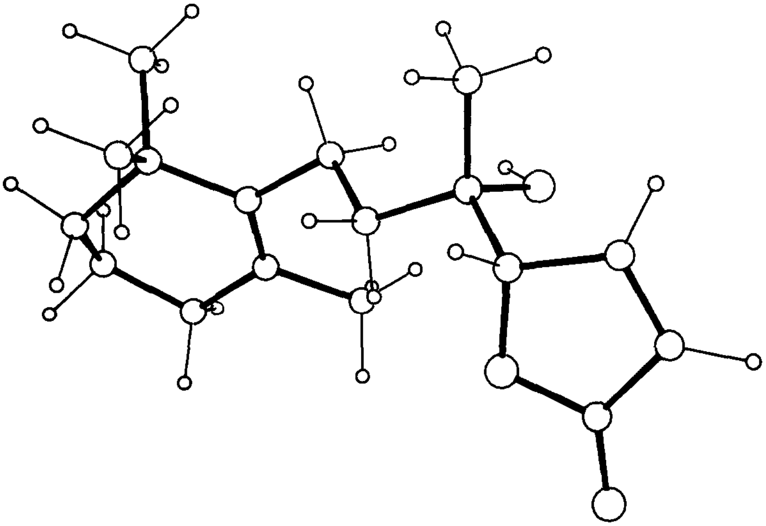


Fig. Perspective drawing of the structure of butenolide 6

In this way, the first synthesis of (±)-cavernosine was achieved in an overall yield of 38% from dihydro-β-ionone. Further applications of 2(5*H*)-furanone-derived enolates as synthons for the regio- and diastereocontrolled construction of natural products will be described elsewhere.

Acknowledgment : We are indebted to the Swiss National Science Foundation (grant No. 2.812-0.85) for financial support.

References and Notes

1) Braekman, J.C.; Daloze, D.; Bertau, R.; Macedo de Abreu, P., *Bull. Soc Chim. Belg.* 1982, *91*, 791.

2) Jefford, C.W.; Jaggi, D.; Boukouvalas, J.; preceding paper.

3) Reduction of β-ionone gives 2 in ca.90% yield: Negishi, E; King, A.O.; Klima, W.L.; Patterson, W.; Silveira, A.,Jr., *J. Org. Chem.* 1980, *45*, 2526; Imamoto, T.; Mita, T.; Yokoyama, M., *J. Chem. Soc. Chem. Commun.* 1984, 163.

4) Silyl ethers derived from aldehydes and 3 are easily hydrolyzed just with water and are therefore not usually detected (cf. ref.2). The ratios of silyl ethers 4/5 and the alcohols 6/7 obtained therefrom are similar.

5) To the best of our knowledge, the $TrClO_4$-induced reaction of silyl enol ethers with ketones has not been reported. For the related reaction with aldehydes see: Mukaiyama, T.; Kobayashi, S.; Murakami, M., *Chem. Lett.*, 1985, 447.

6) Even aldehydes do not react with 1-trimethysiloxycyclohexene under similar conditions (Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.*, 1980, *102*, 3248; *Tetrahedron*, 1981, *37*, 3899). However, 3 reacts as efficiently with ketone 2 as with aldehydes (cf. ref.2).

7) Optimal conditions for eventual reaction are yet to be found. Silyl enol ethers in the presence of F^- fail to react with ketones: Nakamura, E.; Shimizu, M.; Kawajima, I.; Sakata, J.; Yokoyama, K.; Noyori, R., *J. Org. Chem.* 1983, *48*, 932.

8) Compounds, 1, 4+5, 6, 7 and 8 gave satisfactory analytical and spectral data. Erythro alcohols 1 and 7 are colorless oils while threo epimers 8 and 6 have m.p. 68-9° and 118-9° respectively. The chemical shift of the C3 proton, δ7.48 (6) and 7.54 (7) distinguishes 6 from 7 (cf. ref. 2). (±)-Cavernosine (1): ^{1}H-NMR (360 MHz, $CDCl_3$) δ: 0.98 (3H, s), 0.99 (3H, s), 1.24 (1H, bs), 1.34 (3H, s), 1.40 (2H, m), 1.43-1.58 (4H, m), 1.58 (3H, s), 1.83 (2H, bt, J = 6.4 Hz), 1.98-2.30 (4H, m), 2.56 (2H, m), 4.36 (1H, dd, J = 7.5, J = 7.5 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 19.43 (t), 19.74 (q), 21.82 (t), 21.96 (t),23.26 (q), 28.55 (q), 28.68 (q), 29.00 (q), 32.74 (t), 35.06 (s), 36.92 (t), 39.80 (t), 73.12 (s), 85.63 (d), 127.53 (s), 136.21 (s), 177.36 (s). (±)-Epicavernosine (8): ^{1}H-NMR (360 MHz, $CDCl_3$) δ: 1.01 (6H, bs), 1.17 (3H, s), 1.43 (2H, m), 1.56 (2H, m), 1.60 (3H, s), 1.67 (2H, m), 1.74 (1H, bs), 1.90 (2H, bt, J = 6.4 Hz), 2.05-2.31 (4H, m), 2.57 (2H, m), 4.43 (1H, dd, J = 7.4, J = 7.3 Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 19.44 (t), 19.76 (q), 20.57 (q), 22.18 (t), 22.43 (t), 28.62 (q, two overlapping signals), 29.01 (t), 32.74 (t), 35.01 (s), 39.50 (t), 39.76 (t), 73.07 (s), 84.76 (d), 127.52 (s), 136.01 (s), 177.20 (s).

9) Crystallographic data for 6 ($C_{17}H_{26}O_3$): Colorless monoclinic crystal, 0.13 x 0.18 x 0.24 mm; space group $P2_1/c$, a = 20.278(4), b = 6.4312(12), c = 12.769(2) Å, β = 104.38(1)°, V = 1613.2 Å, Z = 4, D_c = 1.146 gcm^{-3}. Measurements made on a Philips PW 1100 four-circle diffractometer, $\mu(\text{Mo-K}_\alpha)$ = 0.072mm^{-1}; 1287 unique reflections of which 774 with $|F| \geq 4\sigma(F)$ and $|F| \geq 8$ were treated as observed by direct methods (MULTAN 80 program); all coordinates of H atoms were calculated except those of the hydroxyl group which were observed by ΔF. Anisotropic refinement converged at R = 0.077. Observed and calculated structure factors may be obtained on request from G.B. Crystallographic data has been deposited at the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.

10) See ref. 2 and Kido, F.; Tsutsumi, K.; Maruta, R.; Yoshikoshi, A., *J. Am. Chem. Soc.* 1979, *101*, 6420; Jacobi, P.A.; Craig, T.A.; Walker, D.G.; Arrick, B.A.; Frechette, R.F. *J. Am. Chem. Soc.* 1984, *106*, 5585.

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