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SYNTHESIS OF ELASNIN[1]

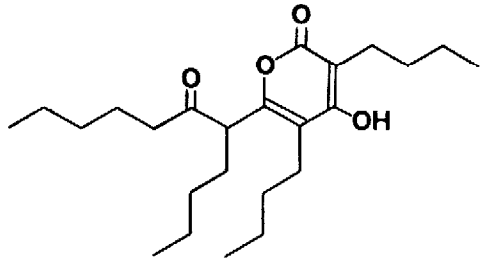
Jürg R. Pfister

Syntex Research, Palo Alto, California 94304

Summary: An efficient synthesis of the naturally occurring elastase inhibitor elasnin is described.

Elasnin (1) is an elastase inhibitor which has been isolated from culture broths of a strain of Streptomyces noboritoensis.[2] Its unique structure, formally related to that of the polyketide tetraacetic lactone,[3] has recently been elucidated.[4]

We report here an effective synthesis of elasnin based on the aldol reaction[5] of a suitably substituted β-ketoester dianion[6] with an α,β-unsaturated aldehyde,[7,8] which permits rapid, convergent assembly of the 24-carbon skeleton of elasnin from the simple C_6 precursors n-hexanal (2) and methyl n-hexanoate (4).

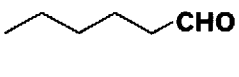


(1)

Accordingly, n-hexanal (2) was subjected to a boric acid catalyzed aldol condensation[9] (xylene, reflux, Dean-Stark separator, 20 hrs) to afford (E)-2-butyl-2-octenal[10] (3; 77% yield[11]) as the first C_{12}-unit.

Conversely, ester condensation of methyl n-hexanoate (4) with 0.5 equiv. NaH in THF (24 hrs reflux, 90%) provided, as the second C_{12}-unit, methyl 2-butyl-3-oxooctanoate[12] (5). The latter was deprotonated successively with NaH (1 equiv. in THF, 50°, 1 hr)[13] and BuLi (1 equiv., 1.6 M in hexane, 0°, 30 min), and the resulting dianion reacted with 3 (added as a THF solution) at 0° for 30 min. Careful work-up (quenching with aq. NH_4Cl, extraction with pentane, rotary evaporation <40°) gave an oil consisting mostly of the desired ketol 6, which was, however, too unstable to be purified efficiently. Oxidation of 6 with DDQ (1.5 equiv., dioxan, reflux, 9 hrs) afforded the enone 7 in a 60% yield for the last two steps.[14,15]

Treatment of 7 with a catalytic amount of p-TsOH in toluene (reflux through A4 molecular sieves for 18 hrs) resulted in the formation of enol lactone 8 (77% yield),[16] which was converted into the corresponding O-acetate 9 by conventional means (Ac_2O-pyridine, RT, 3 hrs,



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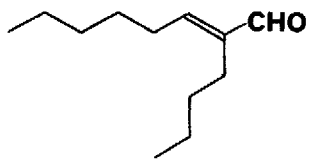

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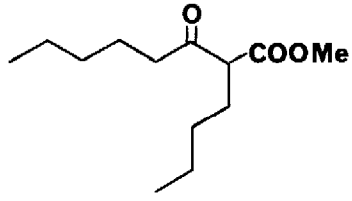

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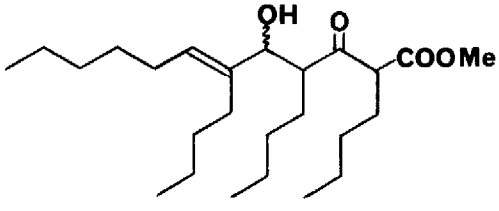

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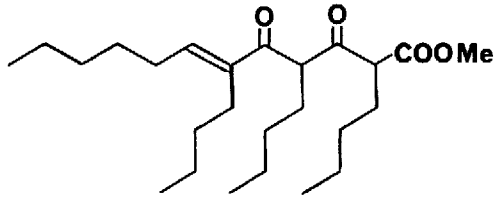

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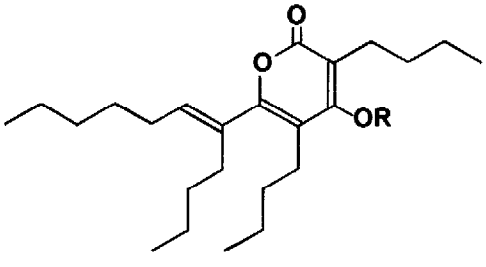
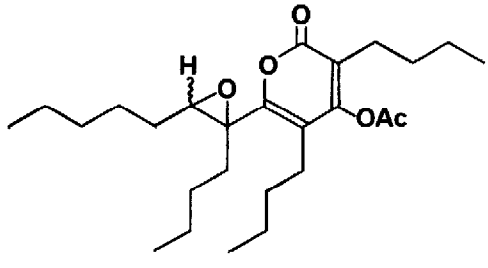


8 R = H
9 R = Ac



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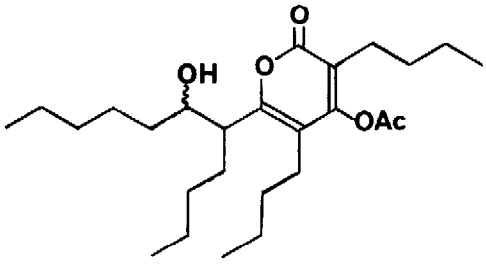

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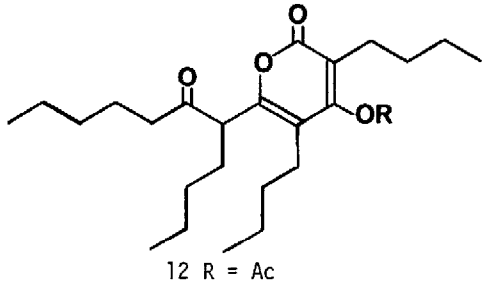

12 R = Ac
1 R = H

85%).[17] Forced epoxidation[18] of 9 with m-chloroperoxybenzoic acid (1.75 equiv.) in the presence of 4,4'-thiobis-(6-t-butyl-3-methylphenol) ($ClCH_2CH_2Cl$, reflux, 9 hrs) gave epoxide 10 (88% yield).[19] As expected, hydrogenolytic oxirane ring opening of 10 (10% Pd-C, EtOH, RT) afforded exclusively the desired secondary alcohol 11, which was oxidized with Jones reagent without any further characterization. The resulting ketone 12 (80% yield from 10) exhibited physical data[20] in close agreement with those published for the compound obtained by acetylation of natural elasnin.[4]

Finally, brief exposure of 12 to conc. H_2SO_4 (0°, 5 min) gave a 92% yield of elasnin (1) with spectroscopic properties[21] in excellent agreement with those derived from an authentic sample of elasnin.[2,4]

Additionally, acidic degradation of 1 (3 N HCl, AcOH, reflux, 72 hrs) gave 3,5-dibutyl-2,6-dipentyl-4H-pyran-4-one[4] as the sole product.

It should be noted that the very low optical rotation ($[\alpha]_D^{19}$ -0.9°, c = 1.0, EtOH) reported[4] for elasnin is probably due to racemization caused by exposure of this material to 0.5 N NaOH during the extraction procedure.[2] Experimentally, we were able to demonstrate that the methine group flanked by carbonyl and pyrone ring is rapidly deuterated (0.5 N NaOD, 4:1 $MeOD-D_2O$, RT).

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References and Notes

1. Contribution No. 545 from the Institute of Organic Chemistry, Syntex Research, Palo Alto, California.
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11. Indicated yields refer to purified compounds (distillation or chromatography) with GC purities >95%.
12. A. N. Kost and F. Gents, Z. Obshch. Khim., 28, 277 (1958); C. A., 53, 9197i (1959).
13. Deprotonation of 5 at RT or below was extremely slow.

14. Satisfactory IR, UV, ^{1}H NMR, ^{13}C NMR, and mass spectra, as well as elemental analyses, were obtained for all new compounds. Partial spectral data for each compound are provided as footnotes.

15. 7: UV (EtOH) 238 nm (log ε 4.0); MS 408 (M^+); ^{1}H NMR (δ, $CDCl_3$) 6.68 (t, J 7 Hz, 1H), 4.42 (m, 2H), 3.68 (s, 3H).

16. 8: UV (EtOH) 220, 300 nm (log ε 4.15, 3.97); MS 376 (M^+).

17. 9: UV (EtOH) 234, 311 nm (log ε 3.1, 3.4); MS 418 (M^+); ^{1}H NMR (δ, $CDCl_3$) 5.68 (t, J 7 Hz, 1H), 2.33 (s, 3H).

18. Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, and H. Kakoi, J. Chem. Soc., Chem. Commun., 64 (1972).

19. 10: UV (EtOH) 220, 299 nm (log ε 3.5, 3.95); MS 434 (M^+); ^{1}H NMR (δ, $CDCl_3$) 3.02 (m, 1H).

20. 12: UV (EtOH) 306 nm (log ε 3.92); IR (neat) 1770, 1715, 1700, 1635 cm^{-1}; MS 434 (M^+); ^{1}H NMR (δ, $CDCl_3$) 3.62 (t, J 7 Hz, 1H), 2.35 (s, 3H).

21. 1: UV (EtOH) 293 nm (log ε 3.89); IR (CCl_4) 3100, 1710, 1675, 1635 cm^{-1}; MS 392 (M^+); ^{1}H NMR (δ, $CDCl_3$) 3.58 (t, J 7 Hz, 1H).

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