Tetrahedron Letters,Vol.27,No.12,pp 1407-1410,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

STEREOSELECTIVE SYNTHESIS OF PTILOCAULIN AND ITS 7-EPIMER[1]

Alfred Hassner*, K.S. Keshava Murthy

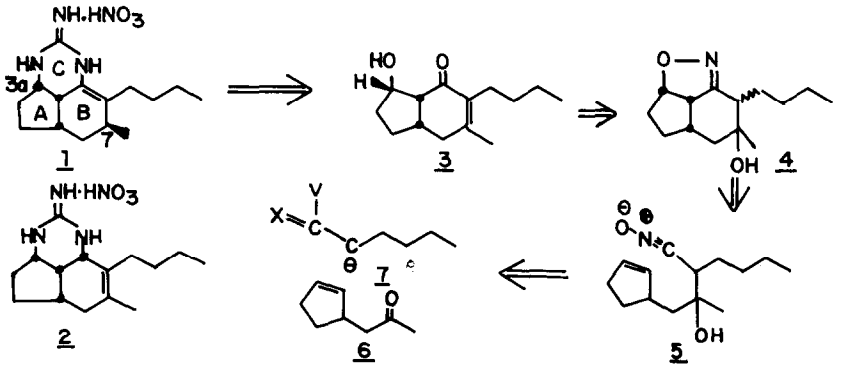
Department of Chemistry, Bar-Ilan University, Ramat-Gan 52100, Israel

Abstract: A versatile stereoselective synthesis of ptilocaulin 1 and its 7-epimer 22, involving formation of the B-ring by intramolecular nitrile oxide cyclization, is described.

Ptilocaulin 1 and isoptilocaulin 2 are antileukemic and antimicrobial agents isolated from marine sponges by Rinehart and coworkers[2]. They possess a simple but unusual structure of a guanidine annelated to a cis hydrindane system. Two syntheses of ptilocaulin 1, which involve fusion of the 5-membered A-ring unto a substituted B-ring, have recently been reported[3,4].

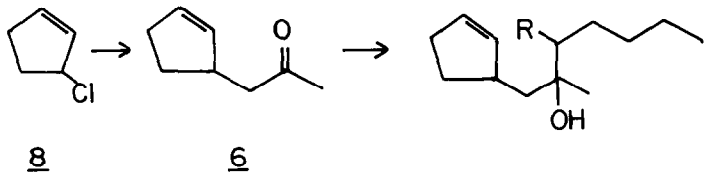
We hereby report an efficient 7 step stereoselective approach to ptilocaulin 1 as well as to its 7-epimer, which involves the stereospecific annelation of the 6-membered B-ring via an intramolecular nitrile oxide - olefin dipolar cycloaddition (INOC)[5]. In the course of our synthesis we also describe a rare example of an aldol condensation involving the reaction of a ketone with a protected aldehyde enolate, in the form of the oxime dianion, to lead to a β-hydroxy aldehyde as the respective oxime, which is very useful for the INOC reaction. The synthesis provides a great deal of versatility for structural changes in the side chains and ring skeleton.

Our retrosynthetic analysis involves the β-hydroxyketone 3 derived from a fused isoxazoline 4, for which we visualized a stereoselective synthesis via the INOC reaction of a nitrile oxide of type 5. The structure of ketone 3 has the advantage of involving only three stereochemical centers that should be formed in one step stereospecifically via the INOC reaction. Furthermore, it may be possible by appropriate stereoselective reductions to introduce the fourth asymmetric center (C-7 of ptilocaulin) and produce either the natural beta methyl configuration or its alpha epimer. 3 should be convertible to the unsaturated ketone 18, which has already been used as a precursor to ptilocaulin by Snider et al[3].



In the next retrosynthetic step we chose oxime 12 as the precursor to the desired nitrile oxide 5. 12 should be derivable by condensation of 7, the α-anion of an ester, an aldehyde or preferably an oxime, with the unsaturated ketone 6. Initially (Scheme 1) we approached our synthesis via a Reformatzky reaction between methyl α-bromohexanoate and the olefinic ketone 6. The latter is readily available in 75% yield by alkylation of acetoacetic ester with 3-chlorocyclopentene 8 followed by decarboxylation[6]. The resulting ester 9 (70%) was reduced with LAH to the alcohol 10 (88%) which was converted by PCC (85%) into the aldehyde 11. Oxiмation of 11 provided 12 (90%).

SCHEME-1



8 6

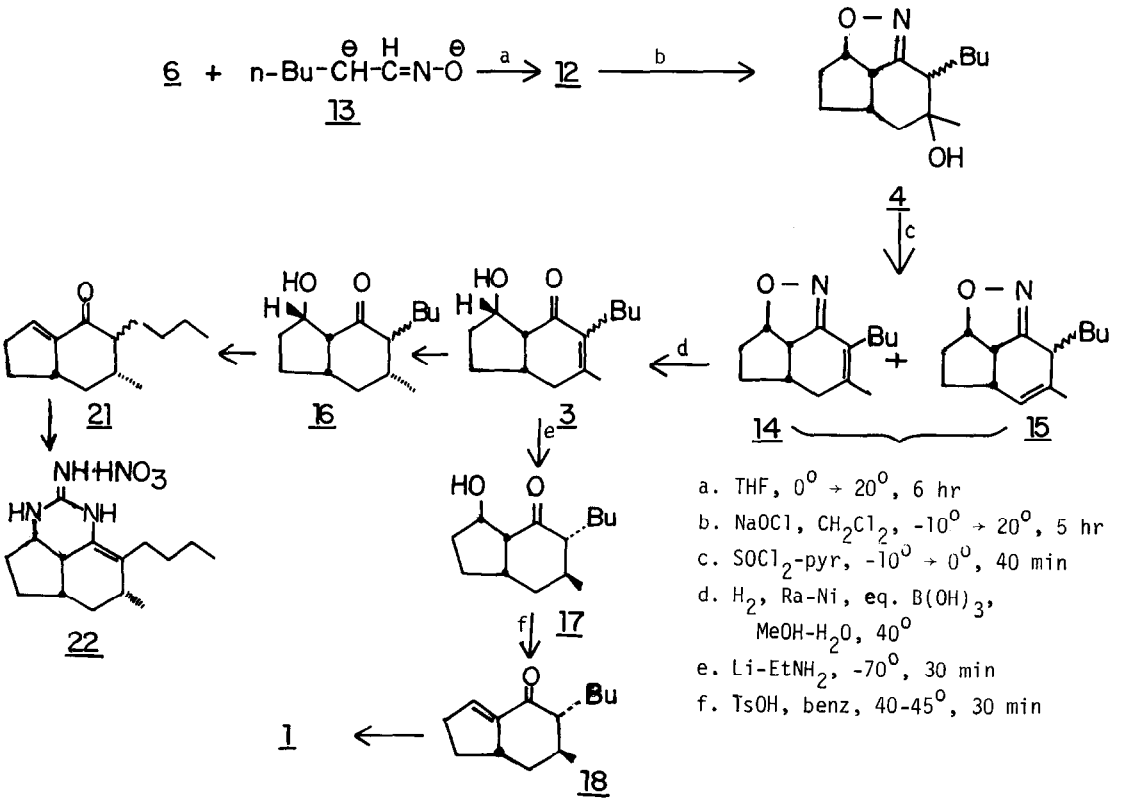
9: R=CO_2Me
10: R=CH_2OH
11: R=CHO
12: R= CH=N-OH

Searching for a more direct route to 12, we attempted the condensation of hexanal oxime dianion 13 (from the oxime with 2 equiv Bu-Li) with ketone 6 and after adjusting the conditions we were able to achieve this direct transformation to 12 in 90% yield (Scheme 2). This promises to be a useful aldol condensation between a masked enolate of an aldehyde with a ketone to form β-hydroxy aldehydes. While many examples are available in the literature for aldol condensations between masked ketone enolates and either aldehydes or ketones, there are few examples of masked aldehyde enolate condensations with ketones[7]. The transformation 6+13 → 12 was particularly useful for us, since our goal was the β-hydroxy aldoxime 12 rather than the free aldehyde 11. Indeed treatment of 12 with NaOCl provided in one step, via a nitrile oxide intermediate 5, the desired tricyclic isoxazoline 4 in 80% yield.

Isoxazoline 4 was formed as a mixture of four diastereomers of which two were isolated pure by chromatography. The mixture of 4 was dehydrated in 95% yield to the unsaturated isoxazolines 14 and 15 (in a 1:1 ratio). That the INOC cyclization had occurred stereospecifically to form three centers in 4 with the desired stereochemistry was clear from H-nmr and ^{13}C-nmr spectra and from the fact that all four diastereomers of 4 produced in this cycloaddition led via Raney Nickel reduction[8] of 14 and 15 to a single isomer of the unsaturated ketol 3 in 60% yield[9]. Ketol 3 was separated by chromatography from some unreacted 14, 15, and other minor ketonic products.

The unsaturated ketol 3 is a key intermediate in the formation of ptilocaulin 1 and of its 7-methyl epimer. Thus H_2-Pd reduction[10] occurred from the convex side to produce the 7α-methyl ketol 16 (95% as two isomers in a 5:1 ratio) while Li-$EtNH_2$ [11] reduction led to the desired 7β-methyl ketol 17 (two isomers in 85% yield) by axial protonation of the intermediate carbanion. Attempts to reduce 3 with Li in liq. NH_3 were not successful and led to overreduction. Finally, dehydration of 17 with tosic acid occurred quantitatively to produce

SCHEME 2



the relay compound 18, which on heating with guanidine affords (±) ptilocaulin 1 isolated as its nitrate salt.

Snider and Faith[3] reported that heating of ketone 18 with guanidine in benzene for 24 hr led almost exclusively to ptilocaulin 1, isolated as its nitrate in 35-40% yield. We find that heating for 10 hr gave isomers 1, 19 and 20 [12], isolated in 50% yield as nitrate salts in a ratio of 5:2:1. Further heating (12-14 hr) in the presence of guanidine converts this mixture into ptilocaulin, as was also observed by Roush and Walts[4]. Hence our yield of 1-nitrate from ketone 18 is effectively 50%.

Employing the same reaction sequence (dehydration, condensation with guanidine and nitric acid salt formation) on the 7α-isomer 16, we obtained 7-epiptilocaulin nitrate 22, as a major component. Our synthetic route permits facile structural modifications, which should be of importance in view of the biological activity of these unusual cytotoxic agents.

Acknowledgement: We thank Dr. H.E. Gottlieb for valuable help and interpretation of nmr spectra. Support of this research by the Israel Cancer Society and the US-Israel Binational Science Foundation (Grant 00117) is gratefully acknowledged.

REFERENCES

1. Stereochemistry 74. For paper 73, see, A. Hassner, D.J. Dillon, K. Onan, Tetrahedron Lett., 24, 1135 (1983).

2. G.C. Harbour, A.A. Tymiak, K.L. Rinehart, Jr., P.D. Shaw, R.G. Hughes, Jr., S.A. Mizak J.H. Coats, G.E. Zurenko, L.H. Li, S.L. Kuentzel, J. Am. Chem. Soc., 103, 5604 (1981).

3. B.B. Snider, W.C. Faith, ibid, 106, 1443 (1984).

4. W.R. Roush, A.E. Walts, ibid, 106, 721 (1984) and A.E. Walts, W.R. Roush, Tetrahedron 41, 3623 (1985).

5. A.P. Kozikowski, Acc. Chem. Res., 17, 410 (1984).

6. J.v. Braun, W. Rudolph, Chem. Ber., 67, 269 (1934).

7. a) W.G. Kofron, M.K. Yeh, J. Org. Chem. 41, 439 (1976), showed that propanaloxime dianion gives a poor yield of benzylation product.

   b) For a review see T. Mukaiyama, Org. React., 28, 203 (1982).

8. D.P. Curran, J. Am. Chem. Soc., 104, 4024 (1982).

9. ^{1}H nmr ($CDCl_3$), δ ppm: (The numbering of carbons in 4, 3, 21, 22 corresponds to the numbering in 1.

   4(mixture of 4 diastereomers, A,B,C,D), A: 5.0 (ddd, J=8,3,1 Hz, C3a-H), 3.50 (dd, J=8,8 Hz, C8b-H), 1.32 (s, C7-Me); B: 5.0 (ddd, J=8,3,1 Hz, C3a-H) 3.53 (dd, J=8,8 Hz, C8b-H), 1.27 (s, C7-Me) C & D: 5.0 (m, C3a-H) 3.72, 3.45 (dd, J=9, 9 Hz, C8b-H) 1.25, 1.3 (s, C7-Me).

   3: 4.44 (m, C3a-H), 3.82 (d, OH), 2.57 (dd J=7, 7 Hz,C8b-H) 1.95 (s, C7-Me)

   21a (trans): 6.49 (m, C3a-H), 0.97 (d, J=6.1 Hz, C7-Me),

   21b (cis): 6.57 (m, C3a-H), 1.04 (d, J=6.1 Hz, C7-Me),

   22: 9.22 (bs, 1H, NH), 8.65 (bs, 1H, NH), 7.74 (bs, 2H, NH_2) 4.23 (m, 1H, C3a-H), 2.5 - 1.05 (m, 14H),1.0 (d, 3H, J=6.4 Hz, C7-Me), 0.89 (t, 3H, J=7.3 Hz, CH_3).

   ^{13}C nmr ($CDCl_3$) δ ppm:

   3: 200.7, 154.6, 136.2, 76.2, 51.6, 35.8, 34.1, 32.8, 31.1, 28.7, 24.6, 22.6, 21.5, 13.7.

   21a trans: 200.5, 144.8, 137.6, 56.3, 44.5, 41.1, 34.2, 33.2, 31.7, 28.4, 26.4, 23.3 20.9, 14.0

   21b cis: 203.1, 144.2, 137.1, 54.4, 45.4, 35.6, 34.2, 33.4, 32.3, 29.7, 24.9, 22.8, 18.5, 14.0

   22: 153.8, 128.0, 117.0, 52.4, 42.6, 39.0, 36.7, 33.0, 32.2, 29.7, 27.2, 26.1, 23.1, 20.0, 14.2.

   ^{13}C, ^{1}H nmr and mass spectral data as well as the melting point of 1 were identical with the literature values[2,3].

10. G. Stork and S. Danishefsky, J. Am. Chem. Soc., 89, 5459 (1967).

11. A.W. Burgstahler, M.E. Sanders, Synthesis, 400 (1980).

12. Isomers 19 and 20 refer to the trans fused and the $\Delta^{8a,8b}$ double bond isomers respectively of 1 (see ref. 4).

(Received in UK 27 January 1986)