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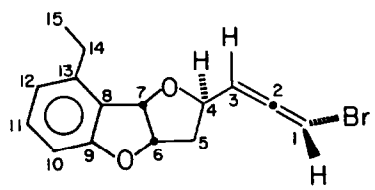
BIOMIMETIC SYNTHESIS OF (±) PANACENE

Ken S. Feldman

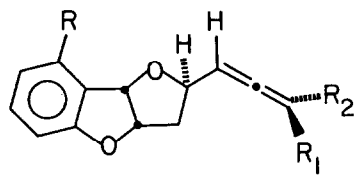
Chemistry Department, Stanford University, Stanford, Ca., 94305

Summary: (±) Panacene 1a and (±) 1-epibromopanacene 1b have been synthesized by a biomimetic brominative cyclization of hydroxyenyne 4.

Panacene is a metabolite of the sea hare Aplysia brasiliana which has aroused interest for both its uncommon bromoallene moiety and its fish antifeedent properties.[1] Recently we described the synthesis of (±) panacene 1a, (±) 1-epibromopanacene 1b, and the corresponding desethyl species (±) 2a and 2b.[2] This work allowed us to assign the relative stereochemistry of the bromoallene portion and thus complete the structural elucidation of panacene.



1a

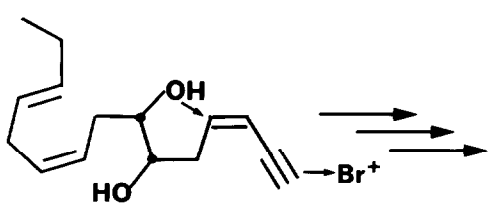


1b R = C_2H_5, R_1 = Br, R_2 = H

2a R = H, R_1 = H, R_2 = Br

2b R = H, R_1 = Br, R_2 = H

In speculating about the biosynthesis of panacene, Meinwald has proposed a brominative cyclization of a 3-hydroxyenyne for the origin of the tetrahydrofurfuryl bromoallene portion.[1] Like other halogenated fatty acid metabolites from A.brasiliana panacene might then originate from successive oxidative cyclizations of laurediol 3:[3]



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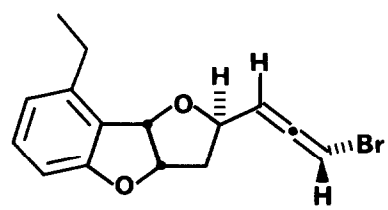
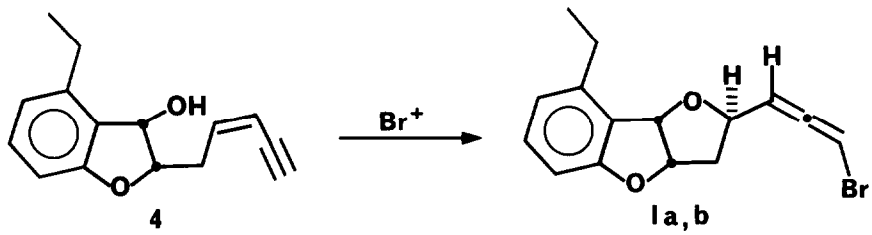
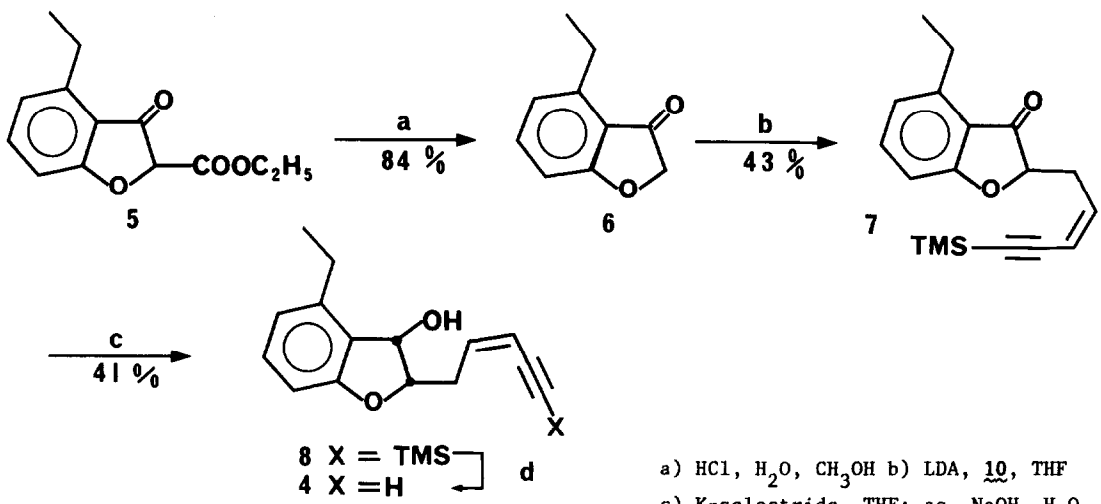


1a

We would now like to report the convergent synthesis of hydroxyenyne 4, and its subsequent biomimetic cyclization to yield panacene and 1-epibromopanacene.[4] The preparation of 4 is described in Scheme I.[5]



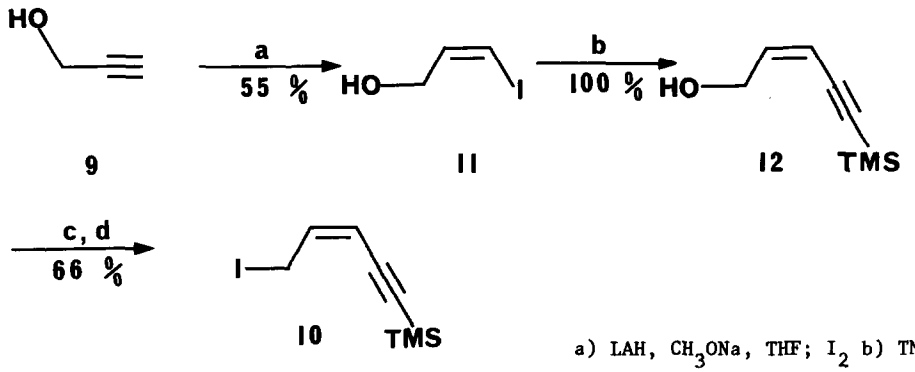
Scheme I



a) HCl, H_2O, CH_3OH b) LDA, 10, THF
c) K-selectride, THF; aq. NaOH, H_2O_2
d) Bu_4NF, THF

The synthesis of 5 has been described previously.[2] The preparation of 1-iodo-5-trimethylsilyl-(Z)-2-penten-4-yne 10 is described in Scheme II. Upon basic oxidative workup of the K-selectride reduction of 7, a mixture of 4 and 8 was obtained. This mixture was directly subjected to desilation followed by chromatography resulting in pure 4 (m.p. 77-77.5 °C).

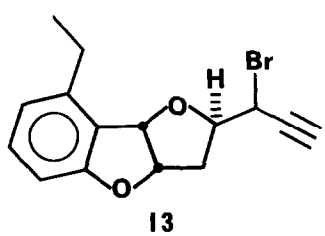
Scheme II



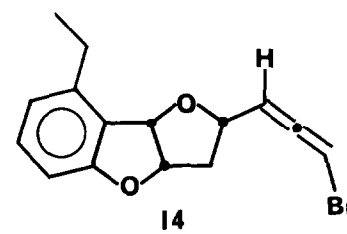
a) LAH, CH_3ONa, THF; I_2 b) TMSC≡CH, Et_2NH, cat. $Pd(PPh_3)_2Cl_2$, cat. CuI[6] c) MsCl, TEA, CH_2Cl_2 d) LiI, THF

The (Z)-iodoalcohol 11 was contaminated with a small amount of the (E) species, but was obtained isomerically pure by spinning band distillation (58-60°C/ 2mm).

Brominative cyclization of 4 (N-bromosuccinimide or 2,4,4,6 tetrabromocyclohexa-2,5-dienone in acetonitrile) led exclusively to a ca. 1:1 mixture of panacene and 1-epibromopanacene, presumably via competitive anti and syn (to the hydroxyl) attack of "Br^+" on the enyne unit (62 %). No evidence of propargylic bromide 13 or the C(4) epimer 14 was detected by ^1H NMR.



13



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The cyclization of 4 to 1 introduces three new elements of structural information: 1) the stereochemistry at C(4), 2) the regiochemistry of bromine addition, and 3) the stereochemistry at C(1). We have demonstrated that the former two features can be completely realized without resorting to enzymic intervention. However, there is as yet no evidence that the stereochemistry at C(1) can be controlled in a nonenzymic cyclization.

Acknowledgment: We would like to thank Dr. E.E. van Tamelen for his support during this work, NSF

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References

1)a) R.B. Kinnel; A.J. Duggan; T. Eisner; J. Meinwald Tetrahedron Lett. 1977, 3913. b) Personal communication from Dr. T. Eisner, Cornell University.

2) In press, J. Am. Chem. Soc.

3) R.B. Kinnel; R.K. Dieter; J. Meinwald; D. van Engen; J. Clardy; T. Eisner; M.O. Stallard; W. Fenical Proc. Nat. Acad. Sci., U.S.A. 1979, 76, 3576. and references therein.

4)a) For other examples of biomimetic brominative cyclizations, see E.E. van Tamelen; E.J. Hessler J. Chem. Soc., Chem. Commun. 1966, 411. b) E.D. Brown; M.D. Solomon; J.K. Sutherland; A. Torre ibid., 1967, 111. c) T. Kato; I. Ichinose; A. Kamoshida; Y. Hirata ibid., 1976, 518 d) T. Kato; I. Ichinose; S. Kumazawa; Y. Hirata Biorg. Chem. 1975, 4, 188.

5) All new compounds exhibited satisfactory ^{1}H NMR, IR, MS and/or combustion analysis.

4: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (t, J = 7.8 Hz, 1H), 6.80 (d J = 7.3 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.26 (dt, J = 10.8, 7.4 Hz, 1H), 5.67 (dd, J= 10.8, 1.3 Hz, 1H), 5.14 (dd, J = 8.4, 5.5 Hz, 1H), 4.45 (dt, J = 7.2, 5.5 Hz, 1H), 3.18 (d, J = 1.8 Hz, 1H). 2.67 (m, 2H), 1.62 (d, J = 8.4 Hz, 1H). IR (neat) 3471,3288,2097 cm^{-1}.

5: m.p.- 44-47 °C. ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.48 (dd, J = 8.3, 7.4 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 6.85 (d, J = 7.3 Hz, 1H), 4.57 (s, 2H), 3.02 (q, J = 7.5 Hz, 2H), 1.24 (t, J = 7.5 Hz, 3H). IR (neat) 1703 cm^{-1}.

7: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (t, J = 8.0 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 6.87 (d, J = 7.4 Hz, 1H), 6.02 (dt, J = 10.8, 7.2 Hz, 1H), 5.66 (d, J = 10.8 Hz, 1H), 4.59 (dd, J = 8.3, 4.7 Hz, 1H), 2.8-3.1 (m, 4H), 0.2 (s, 9H).

12: ^{1}H NMR (100 MHz, $CDCl_3$) δ 6.08 (dt, J = 11.0, ~5.5 Hz, 1H), 5.54 (dt, J = 11.0, 1.4 Hz, 1H), 4.36 (dd, J = 6.2, 1.4 Hz, 2H), 0.2 (s, 9H).

6) K. Sonogashira; Y. Tohda; N. Hagihara Tetrahedron Lett. 1975, 4467.

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