

Stereocontrolled Synthesis of (\pm)-Debromoaplysin and (\pm)-Aplysin

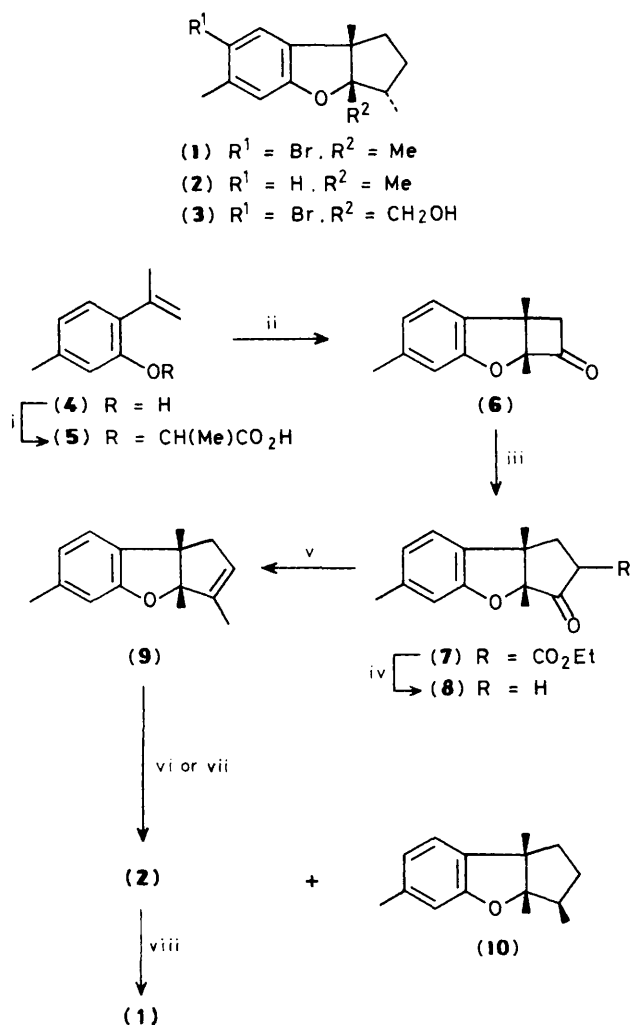
Arun Ghosh, Sujay Biswas, and Ramanathapuram V. Venkateswaran*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta-700032, India

A short and high yield synthesis of the marine sesquiterpenoids Debromoaplysin (**2**) and Aplysin (**1**) is reported involving intramolecular ketene-alkene cycloaddition as a key step.

Aplysin (**1**),¹ the representative compound of the first class of halogenated sesquiterpenes to be discovered from marine sources has been of synthetic interest for several years.² The presumptive precursor of (**1**), debromoaplysin (**2**)¹ and the related alcohol (**3**)³ have also been obtained from marine sources. Previously we have reported⁴ a synthesis of the tricyclic framework of (**1**) through an α -hydroxy-cyclobutane rearrangement. We now report an alternate strategy leading to a short and stereocontrolled synthesis of (**2**) and (**1**) in racemic form in good overall yield.

Alkylation of the styrenol (**4**)⁵ with α -bromopropionic acid



Scheme 1. Reagents and conditions: i, NaH, MeCH(Br)CO₂H, THF, 63%; ii, (a) NaOEt, (b) (COCl)₂, then Et₃N, benzene, reflux, 86%; iii, BF₃·Et₂O, N₂CHCO₂Et, CH₂Cl₂, 81%; iv, LiCl, Me₂SO, H₂O, 160 °C, 92%; v, MeMgI, Et₂O, then POCl₃, pyridine, 88%; vi, Pd/C, EtOH, 99%; vii, PtO₂, EtOH, 99%; viii, Br₂, Na₂CO₃, light petroleum, 75%.

furnished the phenoxyacetic acid (**5**)[†] in 63% yield, m.p. 58–60 °C. Conversion of (**5**) to the corresponding acid-chloride followed by treatment of a benzene solution with Et₃N at reflux resulted in generation of the ketene and concomitant intramolecular cycloaddition⁶ to afford the cyclobutanone (**6**) in 86% yield. Ring expansion of (**6**) with ethyl diazoacetate in the presence of BF₃·Et₂O⁷ furnished the β -keto-ester (**7**) regioselectively in 81% yield which underwent smooth de-ethoxycarbonylation with LiCl in aqueous Me₂SO⁸ to provide the tricyclic ketone (**8**) in 92% yield, enfolding the tricyclic network of (**1**) and (**2**). Reaction of (**8**) with methyl magnesium iodide followed by dehydration delivered the tricyclic alkene (**9**)^{2b,†} in 88% yield. In contrast to reports on dehydroaplysin,^{2a,d} hydrogenation of (**9**) over Pd/C afforded quantitatively a mixture of (\pm)-(**2**) and the isomer (**10**) in 3:2 ratio which could be readily separated by p.l.c. However hydrogenation over PtO₂^{2b} proved highly selective and furnished (**2**) in ca. 97% purity. This was further purified by h.p.l.c. and controlled bromination^{2b} afforded (\pm)-aplysin (**1**), m.p. 98–100 °C (MeOH), (lit. m.p. 100–101 °C)². The identity of synthetic (**2**) and (**1**) was further established from comparing ¹H n.m.r. spectra with those of authentic samples. Thus the present synthesis affords (**1**) in an overall yield of ca. 22% from the styrenol (**4**).

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References

- S. Yamamura and Y. Hirata, *Tetrahedron*, 1963, **19**, 1485.
- (a) K. Yamada, H. Yazawa, D. Uemura, M. Toda, and Y. Hirata, *Tetrahedron*, 1969, **25**, 3509; (b) R. C. Ronald, *Tetrahedron Lett.*, 1976, **49**, 4413; (c) R. C. Ronald, M. B. Gewali, and B. P. Ronald, *J. Org. Chem.*, 1980, **45**, 2224; (d) D. J. Goldsmith, T. K. John, C. D. Kwong, and G. R. Painter, III, *ibid.*, 1980, **45**, 3989.
- J. A. McMillan, I. C. Paul, S. Caccamese, and K. L. Rinehart, *Tetrahedron Lett.*, 1976, 4219.
- D. Sengupta and R. V. Venkateswaran, *J. Chem. Soc. Chem. Commun.*, 1986, 1638.
- K. J. Divakar and A. S. Rao, *Synth. Commun.*, 1976, 423.
- For recent generalisation of this phenomenon see: I. Marko, B. Ronsmans, A. M. Hesbain-Frisque, S. Dumas, L. Ghosez, B. Ernst, and H. Greuter, *J. Am. Chem. Soc.*, 1985, **107**, 2192; B. B. Snider, R. A. H. F. Hui, and Y. S. Kulkarni, *ibid.*, 1985, **107**, 2194; W. T. Brady and Y. F. Giang, *J. Org. Chem.*, 1985, **50**, 5177; W. T. Brady, Y. F. Giang, L. Weng, and M. M. Dad, *ibid.*, 1987, **52**, 2216; B. B. Snider, E. Ron, and B. W. Burbaum, *ibid.*, 1987, **52**, 5413, and references cited therein.
- H. J. Liu and T. Ogino, *Tetrahedron Lett.*, 1973, 4937.
- A. P. Krapcho, *Synthesis*, 1982, **805**, 893.

[†] All compounds reported here gave spectral and analytical data consistent with assigned structures.

[‡] Though this olefin has previously been transformed to (**2**) and (**1**) (ref. 2b) we have been unable to obtain comparison spectra.