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Biomimetic Synthesis of a Preclavulone A Model

E. J. Corey, Kurt Ritter, Miguel Yus and Carmen Nájera

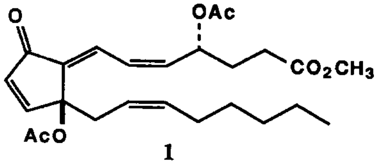
Department of Chemistry, Harvard University, Cambridge, MA, 02138

Summary: A synthetic route to the preclavulone-A (**3**) analogs **11** and **14** via allene oxide and 2-oxidopentadienyl cation intermediates is described which is based on the proposed biosynthesis of **3**.

Clavularia viridis, a Pacific coral which produces the clavulone family of prostanoids (e.g. clavulone I (**1**)), converts arachidonic acid to the probable clavulone precursor preclavulone A (PC-A, **3**)[1] by way of 8-*(R)*-HPETE (**2**).[2] It has been proposed that the biosynthesis of **3** from **2** parallels that for the plant regulator *cis*-jasmonic acid,[3] and proceeds via allene oxide and oxidopentadienyl cation intermediates as outlined in Chart I. This "marine" pathway for prostanoid biosynthesis appears to be widespread in coral having been observed recently in the Atlantic/Caribbean species *Pseudoplexaura porosa*.[4] Indeed several lines of evidence now point to the possibility that the first prostanoid to be observed in a marine source, prostaglandin A_2 methyl ester acetate in *Plexaura homomalla*, arises from the oxidopentadienyl cation pathway[5] rather than the mammalian "endoperoxide" route.[2,6] In the light of this unusual duality of prostanoid biogenesis for marine and mammalian organisms, which has fascinating evolutionary implications, it was of interest to attempt to simulate chemically the allene oxide cyclization (marine) route. The successful realization of this objective is reported herein.

1-Octyne was converted to epoxy alcohol **5** by the sequence: (1) treatment with 1.04 equiv of *n*-butyllithium in tetrahydrofuran (THF) at 0°C followed by reaction with 1.1 equiv of trimethylchlorosilane for 2 h at 23°C to give 1-trimethylsilyl-1-octyne (81%); (2) reaction with 1.1 equiv of diisobutylaluminum hydride in ether at reflux for 1 h followed by addition of 1.1 equiv of methyllithium in ether and further reaction with 4 equiv of dry paraformaldehyde at 25°C for 13 h to afford Z-allylic alcohol **4** (85%)[7]; and (3) oxidation with 1.2 mole % of vanadyl acetylacetonate and 1.05 equiv of *t*-butylhydroperoxide[8] in benzene at reflux for 1.5 h to form **5** (94%). Epoxy alcohol **5** was oxidized with 1.5 mole equiv of pyridinium dichromate in methylene chloride in the presence of powdered 4A molecular sieves with stirring at 23°C for 30 min to generate the corresponding epoxy aldehyde **6** (60%).

Acetylene **7** was synthesized from 1-heptyne by the sequence: (1) treatment with 1 equiv of ethylmagnesium bromide in THF followed by 1 equiv of cuprous cyanide and then coupling with 1-trimethylsilyl-3-iodo-1-propyne (1.1 equiv) at 0°C initially and then 23°C for 4 h to give 1-trimethylsilyl-1,4- decadiyne (81%); (2) hydrogenation at 1 atm with Lindlar catalyst and 1 mole % quinoline in hexane to form 71%



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of 1–trimethylsilyl-deca-4*(Z)*-en-1-yne after purification by silica gel chromatography; and (3) desilylation with potassium fluoride dihydrate in dimethylformamide at 23°C for 4 h to give **7** (85% after distillation at 100°C/0.15 Torr).

1-Heptyne was metalated with 1 equiv of *n*-butyllithium in THF at -78°C for 30 min and treated with epoxy aldehyde **6** for 30 min at -78°C to give, after quenching at -78°C with 1 equiv of propionic acid in methanol and extractive isolation, acetylenic carbinol **8** (*ca.* 70% yield after chromatography on silica gel in the presence of triethylamine). Hydrogenation of **8** (mixture of two diastereomers) with Lindlar catalyst in toluene containing 0.05% pyridine (8 h) afforded *Z,Z*-dienol **9** (91%). Reaction of **9** with 2 equiv of trifluoroacetic anhydride, 2 equiv of triethylamine and 0.1 equiv of 4-dimethylaminopyridine in methylene chloride initially at 0°C and then at 23°C for 1 h produced after extractive isolation and chromatography on silica gel the corresponding trifluoroacetate **10** (88%).

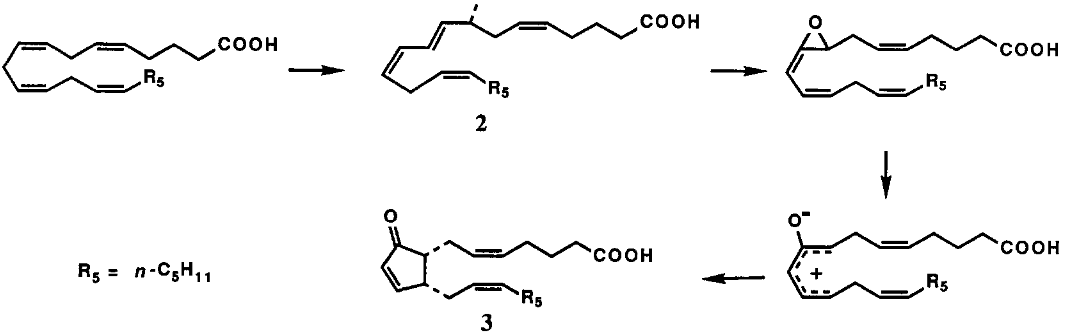
The approach of Chan for the generation of allene oxides[9] by fluoride ion induced[10] desilylation was applied to trifluoroacetate **10**. The choice of fluoride ion source appeared to be critical. The most suitable reagent was found to be anhydrous cesium fluoride (dried at 400°C/0.1 Torr). Reaction of trifluoroacetate **10** with a suspension of finely powdered cesium fluoride in dry acetonitrile under ultrasonic agitation or strong stirring at 23°C for 10-14 h produced three principal products: *cis*-disubstituted cyclopentenone **11** (20-35%), nonadeca-8*(Z)*,10*(E)*-dien-7-one **12** (20-25%) and alcohol **9** (15-20%).[11] Treatment of *cis*-cyclopentenone **11** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF at 23°C for 24 h resulted in isomerization to form predominantly the more stable *trans*-disubstituted cyclopentenone **13**.[13]

The reaction product of the acetylene **7** and epoxy aldehyde **6** was processed in a parallel sequence to give the cyclization product **14**, a closer analog of PC-A.

The formation of the thermodynamically less stable *cis*-cyclopentenone **11** from **10** (or **14** from the corresponding trifluoroacetate precursor) is consistent with the mechanism outlined in Chart I and specifically *antarafacial* pericyclic closure of an oxidopentadienyl cation (which itself is formed from an allene oxide). The demonstration of this process in a chemical system supports the proposition that the pathway of biosynthesis outlined in Chart I is chemically and mechanistically attractive.[14]

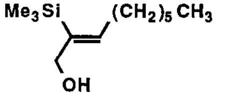
The formation of *Z,E,* dienone **12**[15] in the reaction of trifluoroacetate **10** with cesium fluoride may occur by mechanisms such as those outline in Chart II.

It is possible that the synthesis of *cis*-4,5-disubstituted-2-cyclopentenones described herein can be made more efficient. Among the crucial variables which require study are the desilylation reagent and the anionic leaving group [16,17]



R_5 = n-C_5H_{11}

CHART I



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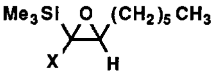
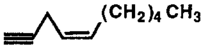


5, X = CH_2OH

6, X = CHO



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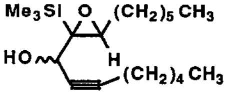

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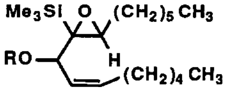
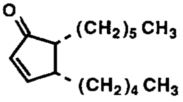
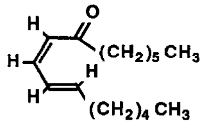


9, R = H

10, R = $COCF_3$



11



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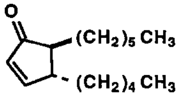

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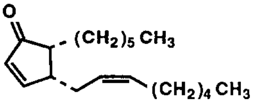

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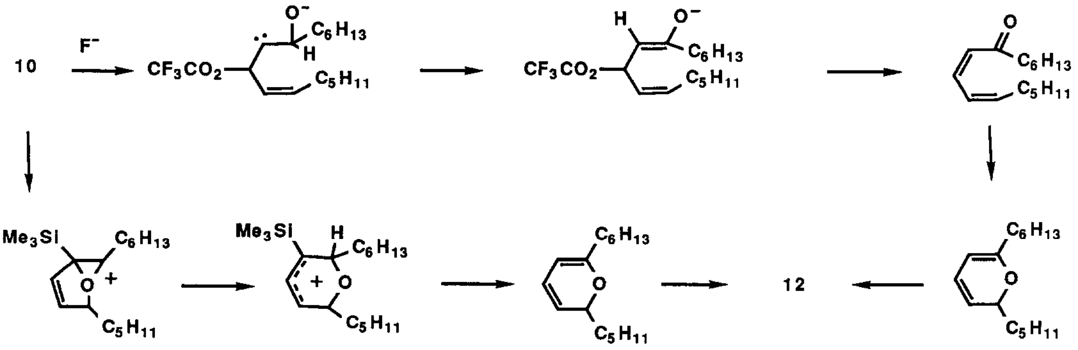

CHART II

References and Notes

1. E. J. Corey and P. T. Lansbury, Jr., *Tetrahedron Letters*, **26**, 4171 (1985). The absolute configuration of PC-A has not yet been determined; **3** is a surmise.
2. E. J. Corey, M. d'Alarcao, S. P. T. Matsuda, and P. T. Lansbury, Jr., *J. Am. Chem. Soc.*, **109**, 289 (1987).
3. (a) B. A. Vick and D. C. Zimmerman, *Biochem. Biophys. Res. Commun.*, **111**, 470 (1983); (b) B. A. Vick, P. Feng and D. C. Zimmerman, *Lipids*, **15**, 468 (1980).
4. E. J. Corey and S. P. T. Matsuda, *Science*, in press.
5. For example, arachidonic acid → 8,15-*bis*-HPETE → 15-hydroxy-8,9-epoxy-5,9,11,13-eicosatetraenoic acid → corresponding 9-oxido-pentadienyl cation → PGA_2.
6. E. J. Corey, H. E. Ensley, M. Hamberg, and B. Samuelsson, *J. Chem. Soc. Chem. Commun.*, 277 (1975).
7. G. Zweifel and H. P. Ong, *Synthesis*, 803 (1980).
8. (a) M. N. Sheng and J. G. Zajacek, *J. Org. Chem.*, **35**, 1839 (1970); (b) K. B. Sharpless, *Aldrichim. Acta*, **12**, 63 (1979).
9. (a) T. H. Chan and B. S. Ong, *Tetrahedron*, **36**, 2269 (1980); (b) T. H. Chan, B. S. Ong and W. Mychajlowskij, *Tetrahedron Letters*, 3253 (1976).
10. E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
11. Yields of products varied considerably in different experiments presumably as a consequence of the heterogeneity of the reaction, variations in the quality of reagents (especially CsF) and the deleterious effect of traces of water. Soluble fluorides such as tetra-*n*-butylammonium fluoride, tris(dimethylamino)sulfonium difluorotrimethyl silicate and benzyltrimethylammonium fluoride[12] were less effective for the transformation of **10** to **11**.
12. See, I. Kuwajima and E. Nakamura, *Accounts Chem. Res.*, **18**, 181 (1985).
13. ^1H NMR data for the diastereomeric enones **11** and **13** are as follows. For **11**, ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 0.89, 0.90$ (tt, 6H, CH_3), 1.25 - 1.72 (m, 18H, CH_2), 2.31 (dt, J = 8.6 Hz, 5.8 Hz, H-5), 2.91 - 2.99 (m, 2H, H-4), 6.15 (dd, J = 5.8 Hz, 1.6 Hz, 1H, H-2), 7.71 (dd, J = 5.8 Hz, 2.8 Hz, 1H, H-3). For **13**, ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 0.89, 0.90$ (tt, 6H, CH_3), 1.25-1.72 (m, 18H, CH_2), 2.31 (dt, J = 8.6 Hz, 5.8 Hz, H-5), 2.91 - 2.99 (m, 2H, H-4), 6.15 (dd, J = 5.8 Hz, 1.6 Hz, 1H, H-2), 7.71 (dd, J = 5.8 Hz, 1H, H-3). The enones **11** and **13** showed infrared absorption (neat) due to carbonyl at 1712 cm^{-1} and ultraviolet absorption (hexane) at 218 (ε 4000) and 327 nm. Tlc mobilities on a silica gel plate were nearly the same, R_f 0.36 (20% ether in hexane).
14. The conversion of allenes to allene oxides and thence to 2-cyclopentenones via 2-oxidopentadienyl cation species, a zwitterionic version of the Nazarov reation, has been known for some time. See, J. Grimaldi and M. Bertrand, *Tetrahedron Letters*, 3269 (1969) and *idem., Bull. Soc. Chim. France*, 957 (1971)
15. The structure of dienone **12** (R_f 0.70, 20% ether in hexane) is clear from the following physical data. ^1H NMR ($CDCl_3$, 270 MHz): $\delta = 0.90$ (tt; 6H, CH_3), 1.20 - 1.72 (m, 20H, CH_2), 2.21 (dt, J = 7.3 Hz, 7.0 Hz, 2H, H-5), 2.45 (t, J = 7.3 Hz, 2H, H-1'), 5.91 (d, J = 11.3 Hz, 1H, H-1), 6.11 (dt, J = 15.2 Hz, 7.0 Hz, 1H, H-4), 6.37 (dd, J = 11.3 Hz, 11.0 Hz, 1H, H-2), 7.36 - 7.46 (m, 1H, H-3). FT-IR (neat, cm^{-1}): 2955, 2925, 2854, 1686, 1630, 1580, 1259, 1127, 1078, 1023, 962, 798. UV (λ_{max} (nm), (ε), ethanol): 216(7,800), 275(12,500). MS (70 eV): m/e = 179 (100%, $C_{12}H_{19}O^+$), 95 (4%), 81 (5%).
16. Although trifluoroacetate is the best anionic leaving group found thus far, mesylate may be superior. The acetate and 2,6-dichlorobenzoate groups were found to be insufficiently activating.

17. This research was assisted financially by grants from the National Institutes of Health and the National Science Foundation. A NATO postdoctoral grant to Kurt Ritter is also gratefully acknowledged.

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