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ENANTIOSELECTIVE TOTAL SYNTHESIS OF (-)-PRECLAVULONE-A

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Summary: An enantio- and stereospecific synthesis of **2**, corresponding to the marine eicosanoid, (-)-preclavulone-A, is reported.

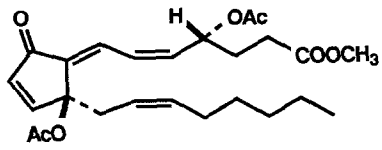
Preclavulone-A was originally detected by radiotracer methods as a metabolite of arachidonic acid in the Pacific coral *Clavularia viridis* which produces the clavulone family of prostanoids, e.g. clavulone I (**1**).[1] Chemical and synthetic studies allowed the assignment of structure **2** (or enantiomer) to preclavulone-A, but the absolute configuration could not be determined since the amounts of this compound which were obtained were less than 10^{-15} g.[1] In the meantime preclavulone-A has been detected as a product of arachidonic acid metabolism in the Atlantic coral *Pseudoplexaura porosa*,[2] and also in many other unrelated species of coral,[3] making it seem likely that this prostanoid is widely synthesized in corals perhaps as a predecessor of a number of more elaborate bioactive prostanoids. In order to facilitate ongoing biosynthetic studies and to ascertain the absolute configuration of preclavulone-A, we have developed an efficient and enantioselective synthesis of **2** which is the subject of this paper.

(-) *(1S,2S)*-5-Norbornene-2-carboxylic acid was conveniently synthesized by titanium tetrachloride-catalyzed Diels-Alder reaction between cyclopentadiene and *(R)*-pantolactone acrylate ester as previously described [4] and converted to the 2-*endo* methyl ketone **3** by reaction with 3 equiv of methyllithium at -25°C initially and then at 0°C for 1 h (89% yield after extractive isolation[5] and filtration through a column of silica gel). Reaction of **3** with 2 equiv of lithium diisopropylamide and 2.3 equiv of trimethylchlorosilane in tetrahydrofuran (THF) at -78°C for 1.5 h produced the trimethylsilyl enol ether **4** in 96% yield. Heating of enol ether **4** as a 10% solution in toluene at 200°C for 4 h in a base-washed sealed Pyrex tube[6] resulted in Cope rearrangement to form tetrahydroindene **5** (*ca.* 80%).[7] Oxidation of **5** (not purified) with 1.1 equiv of *m*-chloroperbenzoic acid in the presence of 4 equiv of sodium bicarbonate in methylene chloride at -5°C for 1 h followed by treatment with a mixture of 5 equiv of 48% aqueous

hydrofluoric acid and 5 equiv of triethylamine in methylene chloride at 0° for 1 h produced hydroxy ketone **6** as major product together with the epimeric alcohol as minor product (ratio 6 : 1, total yield 61% overall from **3**). Oxidative cleavage of the mixture of **6** and its epimer using 1.1 equiv of lead tetraacetate in methanol[8] at -5°C for 1 h provided methyl ester aldehyde **7** (72% yield).

Chain extension of **7** to form diene ester **8**, $[\alpha]_D^{22}$ +74.7° (c=0.72 in THF), was effected in 92% yield by reaction with the Wittig reagent from *n*-hexyltriphenylphosphonium bromide (1.6 equiv) and potassium hexamethyldisilazide (1.5 equiv) in THF at -85°C initially, then at -85°C to 0°C for 1 h and finally at 0°C for 1 h. Saponification of **8** using 4 : 3 : 5 1 N lithium hydroxide in water-methanol-THF at 23°C for 24 h gave the corresponding carboxylic acid which was treated with 3 equiv of iodine in 1 : 1 5% aqueous sodium bicarbonate-THF at 0°C for 2.5 h to give iodo lactone **9** as the only product. Diene lactone **10** was produced from **9** by reaction with 2 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dimethoxyethane at reflux for 12 h, $[\alpha]_D^{22}$ +11.4° (c=1.5 in THF), 89% overall from **8**. Reduction of **10** with 2 equiv of diisobutylaluminum hydride in methylene chloride at -78°C for 40 min afforded the corresponding lactol (**11**, 97%) which was treated with the Wittig reagent from 5-triphenylphosphonio-pentanoic acid bromide (6 equiv) and potassium hexamethyldisilazide (12 equiv) in THF at 25°C for 2 h to give hydroxy acid **12**. Esterification of **12** with ethereal diazomethane gave the methyl ester **13**, $[\alpha]_D^{20}$ -50.1° (c=1.77 in THF) in 84% yield from **10**. Oxidation of **13** with excess Martin's periodinane reagent[9] (in methylene chloride at 23°C for 1 h) furnished enone ester **14**, $[\alpha]_D^{20}$ -131.8° (c=1.14 in THF), in 98% yield. Similarly oxidation of hydroxy acid **12** produced **2** in 89% yield. The 500 MHz ^{1}H NMR, infrared, ultraviolet and mass spectra of synthetic ester **14**[10] were identical with those measured for a sample of preclavulone-A methyl ester obtained from *Pseudoplexaura porosa* as previously described.[2]

The enantio- and stereospecific process described above for the synthesis of **2** makes this substance readily available for chemical or biological studies. The synthesis has been used to prepare (±)-**2** and, obviously, is useful for obtaining the enantiomer of **2**. As mentioned in the introduction preclavulone-A is biosynthesized by many different coral species. The role of preclavulone-A as a precursor for the biosynthesis of other prostanoids, e.g. prostaglandin A_2 methyl ester acetate in *Plexaura homomalla*, is of great interest. One simple possibility for the biosynthesis of prostaglandin A methyl ester acetate from **2** is by a lipoxygenase type of allylic oxygenation which removes hydrogen from C(13) of **2** or the isomeric β,γ-enone and delivers oxygen to C(15) with formation of an *E* 13,14-double bond.[11]



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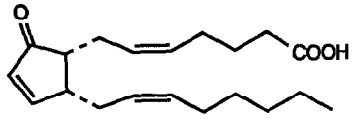

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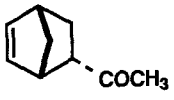

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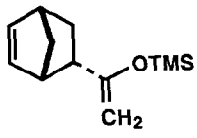

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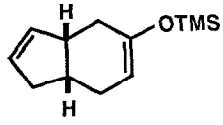

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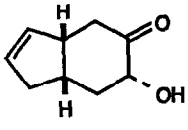

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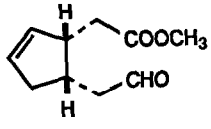

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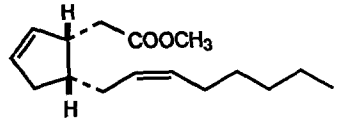

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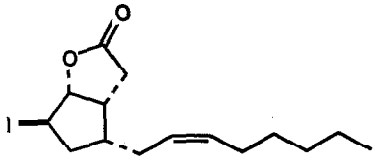

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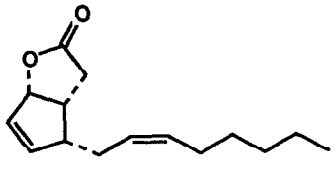

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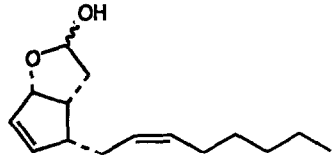

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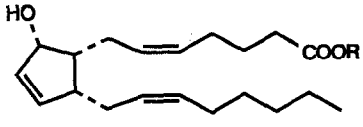
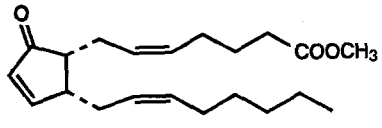


12 R = H
13 R = CH_3



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1. (a) E. J. Corey, P. T. Lansbury, Jr., and Y. Yamada, *Tetrahedron Letters*, **26**, 4171 (1985); (b) E. J. Corey, M. d'Alarcao, S. P. T. Matsuda, P. T. Lansbury, Jr., and Y. Yamada, *J. Am. Chem. Soc.*, **109**, 289 (1987).

2. E. J. Corey and S. P. T. Matsuda, *Tetrahedron Letters*, **28**, 4247 (1987).

3. E. J. Corey, S. P. T. Matsuda, M. B. Cleaver, and R. Nagata, unpublished work.

4. T. Poll, A. Sobczak, H. Hartmann, and G. Helmchen, *Tetrahedron Letters*, **26**, 3095 (1985).

5. The reaction mixture was treated with trimethylchlorosilane at 0°C for 10 min followed by aqueous ammonium chloride; see G. M. Rubottom and C. Kim, *J. Org. Chem.*, **48**, 1550 (1983). Satisfactory ^{1}H NMR, infrared and mass spectral data were obtained for each synthetic intermediate.

6. It is important that the Pyrex tubing be basic to prevent silyl ether cleavage. The Pyrex tubes used in our experiments had been soaked in 35% aqueous potassium hydroxide for 10 days, washed with deionized water and dried in an oven prior to use.

7. See, E. J. Corey and J. E. Munroe, *J. Am. Chem. Soc.*, **104**, 6129 (1982).

8. J. R. Hazen, *J. Org. Chem.*, **35**, 973 (1970).

9. D. B. Dess and J. C. Martin, *J. Org. Chem.*, **48**, 4155 (1983).

10. Spectroscopic data for **14**: ^{1}H NMR: (500MHz, $CDCl_3$) δ 7.67 (dd, J=5.8, J=2.7, 1H), 6.18 (dd, J=5.8, J=1.7, 1H), 5.51-5.36 (m, 4H), 3.65 (s, 3H, OCH_3), 3.02 (m, 1H, HC(12)), 2.52 (dt, J=14, J=4.8, 1H), 2.48-2.40 (m, 2H), 2.31 (t, J=7.5, 2H, CH_2COOMe), 2.16 (dd, J=14, J=8.1, 1H), 2.09 (quintet, J=7, 2H), 1.96 (dt, J=14, J=7.5, 2H), 1.91 (dd, J=11, J=8.5, 1H), 1.70 (d-quintet, J=2, J=7.5, 2H), 1.32 (quintet, J=7.5, 2H), 1.27 (m, 4H), 0.88 (t, J=7, 3H). IR: (neat) 3008, 2954, 2929, 2871, 2857, 1739 (COOMe), 1710 (CO), 1458, 1436, 1347, 1244, 1213, 1197, 1169 cm^{-1}. MS: (EI) m/e 333 (12/M^+ + 1), 332 (3/M^+), 301 (6/M^+ - OCH_3), 192 (10), 121 (11), 82 (100).

11. This research was assisted financially by grants from the National Institutes of Health and the National Science Foundation.

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