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SYNTHESIS OF CLAVULONES (CLAVIRIDENONES)

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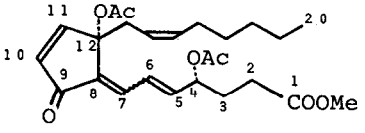
Summary: New marine eicosanoid clavulones (claviridenones) were synthesized from the Corey lactone and D-glutamic acid.

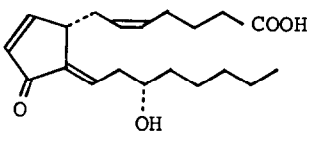
In 1982 new eicosanoids, clavulones (claviridenones), were isolated from the Okinawan soft coral Clavularia viridis[1]. These compounds have attracted much attention, because of these remarkable cytotoxity[2] and a structural resemblance to a highly cytotoxic metabolite of PGD_2, 9-deoxy-Δ^9,Δ^{12}-13,14-dihydro-PGD_2 3[3]. Recently, the synthesis of the racemates had been accomplished by Corey and his co-workers[4], and of the natural ones by Yamada and his co-workers[5].

Herein, we described an efficient and stereospecific synthesis of clavulones (claviridenones) from the prostaglandin-synthetic intermediate, the Corey lactone.



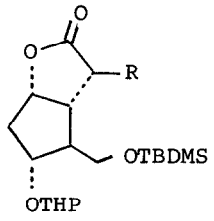
1 5E,7E Clavulone II (Claviridenone-c)

2 5E,7Z Clavulone III (Claviridenone-b)

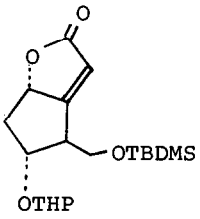


3 9-Deoxy-Δ^9,Δ^{12}-13,14-dihydro PGD_2

The hydroxy group at C-12 position, which is lack in the primary prostaglandin structure, was introduced stereoselectively as described follows. The Corey lactone 4 was converted to the α-phenylselenyl lactone 5[6] (LDA, PhSeCl, THF, -78 °C, 30 min, 86%), which on oxidation gave the α,β-unsaturated lactone 6 (10% aq. H_2O_2, CH_2Cl_2, reflux, 1 h, 79%). The compound 6 was transformed to the allylic alcohol 7 in 86% yield by diisobutylaluminum hydride reduction (toluene, 0 °C, 30 min). The double bond of compound 7 was then oxidized stereoselectively by t-BuOOH (2.0 equiv) in the presence of vandium



4 R = H
5 R = SePh



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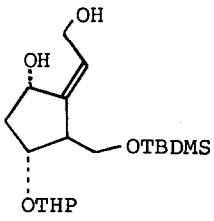

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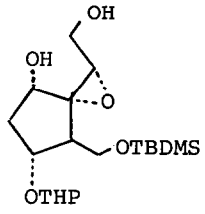

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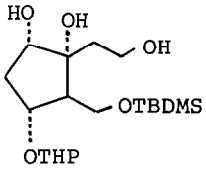

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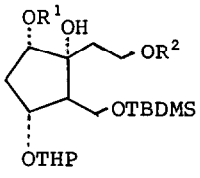
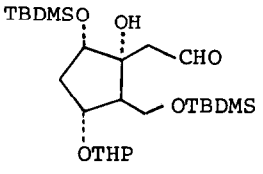


10 R^1=H R^2=COPh
11 R^1=TBDMS R^2=COPh
12 R^1=TBDMS R^2=H



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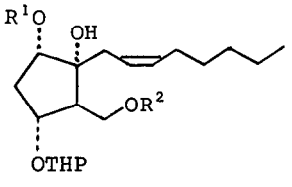
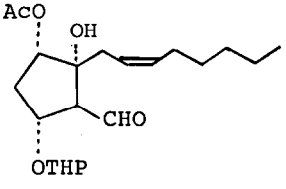


14 R^1=R^2=TBDMS
15 R^1=H^2 R^2=TBDMS
16 R^1=Ac R^2=TBDMS
17 R^1=Ac R^2=H



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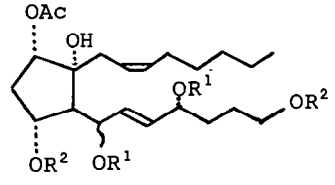
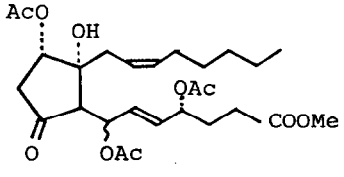


19 R^1=H R^2=THP
20 R^1=Ac R^2=THP
21 R^1=Ac R^2=H



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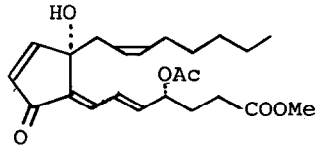

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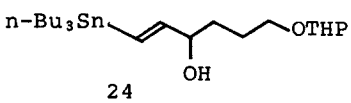

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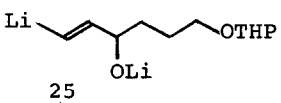

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catalyst[7] to the epoxide 8 in 83% yield. The reductive ring opening of the compound 8 was proceeded highly regioselectively using Red-Al (6 equiv)[8] in THF (0 °C, 30 min) to afford the desired triol 9 as a sole product in 60% yield. The cis-configuration of the *vic*-diol at C-11 and C-12 was confirmed by forming an acetonide in the compound 10 (*vide post*).

To introduce the C-15 to C-20 unit, the triol 9 was converted to the C-9 protected aldehyde 13 in 4 steps: 1) benzoylation of the primary alcohol of the compound 9 (PhCOCl, Py., CH_2Cl_2, -20 °C, 1 h, 66%), 2) protection of the secondary alcohol of the compound 10 by TBDMS (t-BuMe_2SiCl, imidazole, DMF, 25 °C, 18 h, 90%), 3) de-benzoylation of the compound 11 (K_2CO_3, MeOH, 40 °C, 1 h, 94%), and 4) Collins oxidation of primary alcohol of compound 12 (0 °C, 15 min, 64%).

Witting reaction of the aldehyde 13 with n-hexylidene triphenylphosphorane in THF-HMPA (10:1, -78 °C to 25 °C) was proceeded in 79% yield to afford the compound 14 and its olefinic isomer in 2 to 1 ratio. Treatment of the compound 14 by an equimolar amount of tetrabutylammonium fluoride (TBAF) in THF at 0 °C did not cleave the primary silyl ether but the secondary one to affort the compound 15 in high selectivity (70%). And thus obtained secondary alcohol 15 was protected as an acetate (Ac_2O, Py., 25 °C, 2.5 h, 96%) to afford the compound 16. The silyl protective group of compound 16 was then removed by TBAF in THF at 0 °C to afford the primary alcohol 17 (95%), which was then oxidized to the aldehyde 18 by Collins reagent at 0 °C (75%).

The vinyl stannane 24, the C-1 to C-6 unit, was easily prepared from D-glutamic acid[9].

The aldehyde 18, the C-7 to C-20 unit, was finally coupled in THF at -78 °C with the vinyl anion 25, which was derived form the vinyl stannane 24 by treatment with n-BuLi in THF (-20 °C, 2 h), to afford the allylic alcohol 19 (32%). The compound 19 was converted to 20 by acetylation (Ac_2O, Py., 25 °C, 18 h, 45%), and acidic hydrolysis of the THP groups (AcOH:H_2O, 3:1, 80 °C, 8 min) of the compound 20 afforded the diol 21 (65%), as a mixture of diastereoisomer of C-7 alcohol. The diol 21 was oxidized by Jones reagent (-20 °C, 30 min), and subsequently treated with ethereal diazomethane to afford the keto ester 22. The oxidation of C-9 alcohol to ketone was expected to make the two acetoxy groups at C-7 and C-11 labile. Actually, slow elution of the compound 22 through a standard silica gel column produced the fairly stable conjugated polyenone system 23 (43% overall yield from 21), as a mixture of olefinic isomers of the newly formed double bond. Finally, 1 and 2 were obtained by the acetylation of the tertially alcohol at C-12 (Ac_2O, Py., 30 °C, 18 h) of the compound 23, followed by HPLC separation in 2 to 1 ratio (77% total yield).

The clavulones (claviridenones) 1 and 2 obtained were identical with natural clavulone II (claviridenone-c) and III (claviridenone-b), respectively.

Acknowledgement: We are grateful to Professor I. Kitagawa for his kindness to identify our samples to the natural ones.

References and Notes

1) a) H. Kikuchi, Y. Tsukitani, K. Iguchi, and Y. Yamada, Tetrahedron Lett., 23, 5171 (1982). b) M. Kobayashi, T. Yasuzawa, M. Yoshihara, H. Akutsu, Y. Kyogoku, and I. Kitagawa, ibid, 23, 5331 (1982).

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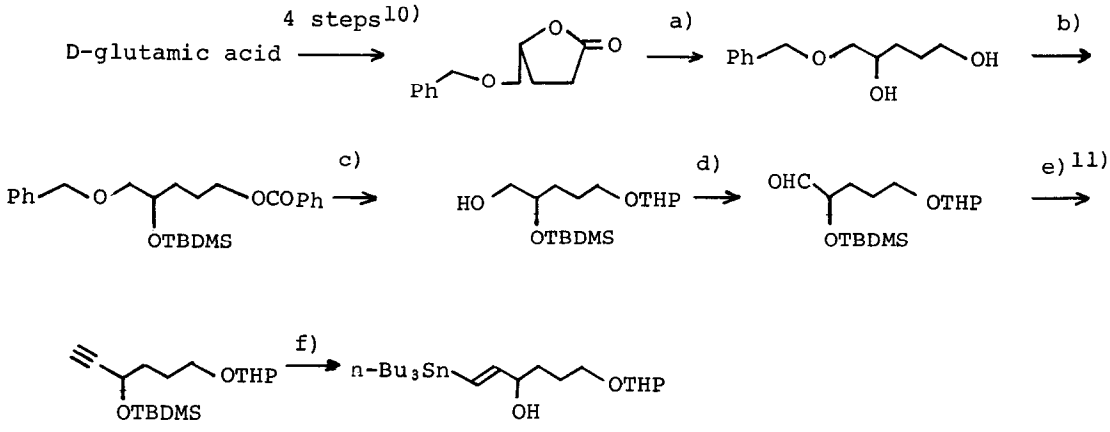
5) H. Nagaoka, T. Miyakoshi, and Y. Yamada, Tetrahedron Lett., 33, 3621 (1984).

6) All new compounds were characterized by full spectroscopic and analytical or exact mass data.

7) a) K.B. Sharpless and R.C. Michaelson, J. Am. Chem. Soc., 95, 6136 (1973). b) S. Tanaka, H. Yamamoto, H. Nozaki, K.B. Shapless, R.C. Michaelson, and J.D. Cutting, ibid, 96, 5254 (1974).

8) S.M. Viti, Tetrahedron Lett., 23 4541 (1982).

9) Compound 14 was prepared from D-glutamic acid by the following sequence:



a) LAH, b) i) PhCOCl, Py., ii) TBDMS-Cl, imidazole, c) i) K_2CO_3/MeOH, ii) DHP, H^+, iii) Raney Ni, d) Collins ox., e) i) Ph_3P, CBr_4, ii) n-BuLi, f) i) n-Bu_3SnH, ii) TBAF

10) M. Taniguchi, K. Koga, and S. Yamada, Tetrahedron, 30, 3547 (1974).

11) E.J. Corey and P.L. Fuchs, Tetrahedron Lett., 3769 (1972).

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