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SYNTHESIS OF A HALOGENATED CLAVULONE ANALOG

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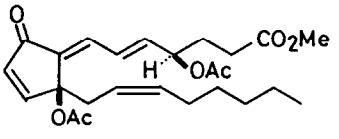
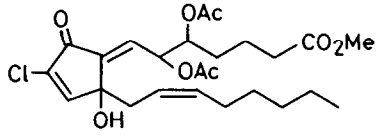
Summary: A halogenated clavulone analog 1 which has remarkable antitumor activity was synthesized in a stereoselective and enantioselective manner.

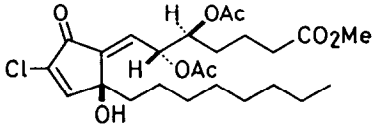
We have described the structures of novel marine prostanoids clavulone I, II, III, IV and their congeners, which are noted by their strong antitumor activity, isolated from Japanese Stlonifer Clavularia viridis,[1] and also have reported an effective and enantioselective total synthesis of clavulones.[2] Recently chlorinated marine prostanoids punaglandins, whose structures are similar to those of clavulones, were isolated from Hawaiian octocoral by P.J.Scheuer et al., and the antitumor activities of these chlorinated prostanoids are stronger than those of clavulones.[3] Their superior biological property caused by introduction of chlorine atom into the cyclopentenone moiety prompted us to study the synthesis of halogenated clavulone analogs. In this



Clavulone II



Punaglandin



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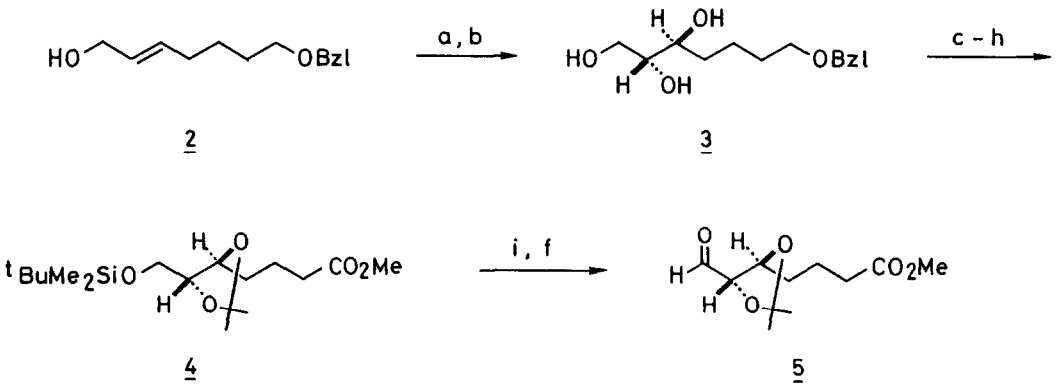
paper we wish to describe an effective synthesis of 10-chlorinated clavulone analog 1.[4]

The synthesis leading to 1 follows that initially ω side-chain was introduced into 4-(S)-hydroxy-2-cyclopenten-1-one (6), then the cyclopentenone moiety was chlorinated, and finally a chiral aldehyde 5 (α side-chain equivalent) was condensed to the chlorinated cyclopentenone using aldol reaction.

The aldehyde 5 was synthesized as outlined in Scheme 1. The allyl alcohol 2[5,6] was converted to the optically active triol 3, $[\alpha]_D$ -0.58° (c=1.04, MeOH), by Sharpless method[7] in 64% yield from 2. After protection of the three hydroxyl groups in 3 as t-butyldimethylsilyl ether for the primary alcohol and acetonide for the two secondary alcohols, it was transformed into the corresponding ester 4, $[\alpha]_D$ -4.6° (c=0.56, $CHCl_3$), by four steps (i. deprotection of the benzyl group, ii. and iii. stepwise oxidation, iv. methylation), in 75% overall yield from 3. Removal of t-butyldimethylsilyl group in 4 followed by Swern oxidation gave the aldehyde 5, which was used for the next aldol condensation with the cyclopentenone 9 immediately, in 85% yield from 4.

The synthesis of 1 was completed as outlined in Scheme 2. Reaction of the cyclopentenone 6, $[\alpha]_D$ -87.5° (c=3.10, $CHCl_3$)[lit.[8] -69.0° (c=2.50, $CHCl_3$)], prepared from L-(+)-diethyl tartrate according to the known procedure,[8] with 2.1 equiv of n-octyl lithium in THF at -78°C for 20 min gave highly stereoselectively the syn-diol 7, $[\alpha]_D$ -65.9° (c=0.54, $CHCl_3$), in 84% yield. After

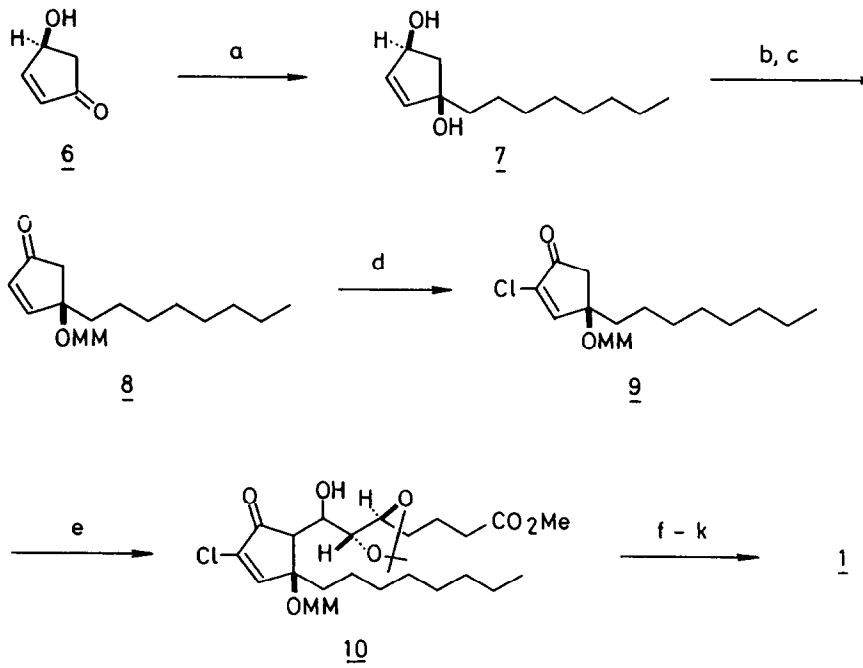
Scheme 1



a) t-BuOOH, $(i\text{-PrO})_4Ti$, L-(+)-diethyl tartrate, CH_2Cl_2, -20°C; b) 0.5N NaOH in H_2O-t-BuOH (5:1), 70°C; c) $t\text{-Bu(Me)}_2SiCl$, imidazole, DMF, 0°C; d) 2,2-dimethoxypropane, dl-CSA, 0°C; e) Li, liq NH_3-THF, -34°C; f) DMSO, $(COCl)_2$, CH_2Cl_2, -78°C and then Et_3N; g) Jones reagent, acetone, 0°C; h) CH_2N_2, Et_2O, 0°C; i) $n\text{-Bu}_4NF$, THF, rt.

oxidation of the secondary hydroxyl group in 7, the tertiary hydroxyl group was protected as methoxymethyl ether to give the cyclopentenone 8, $[\alpha]_D$ -42.0° (c=2.00, $CHCl_3$), in 78% yield from 7. Chlorination of 8 was carried out by bubbling chlorine gas through ether solution at room temperature followed by treatment with excess amount of triethylamine to produce the 10-chlorinated cyclopentenone 9, $[\alpha]_D$ -47.4° (c=0.78, $CHCl_3$) in 82% yield. The enone 9 was added dropwise to 1 equiv of lithium diisopropylamide in THF at -78°C, and after 15 min the resulting enolate was treated with 1 equiv of formerly prepared aldehyde 5 at -78°C for 15 min to give the expected aldol 10[9] as a single isomer in 56% yield (the yield based on the consumed enone 9 was 89%). The

Scheme 2



a) 2.1 equiv of n-octyl lithium, THF, -78°C; b) Jones reagent, acetone, 0°C; c) $ClCH_2OMe$, i-Pr_2NEt, $ClCH_2CH_2Cl$, 60°C; d) Cl_2 gas, Et_2O, rt and then excess Et_3N; e) 1.0 equiv of LDA, THF, -78°C and then 5, -78°C; f) Ac_2O, py, 70°C; g) 4:1 AcOH-H_2O, 80°C; h) CH_2N_2, Et_2O, 0°C; i) Ac_2O, py, 70°C; j) 4:1 AcOH-H_2O, 100°C; k) CH_2N_2, Et_2O, 0°C.

resulted aldol 10 was converted into the desired compound 1[10] by six steps (i. dehydration, ii. hydrolysis of the acetonide,[11] iii. methylation, iv.

acetylation of the two hydroxyl groups at C-5 and C-6 position, v. deprotection of the methoxymethyl group,[11] vi. methylation) in 43% overall yield from 10. This synthetic procedure provides the access of total synthesis of punaglandins.

The 10-chlorinated clavulone analog 1 thus obtained inhibited 10 times the growth of melanoma B16 cells as compared with clavulone II. The IC50 value for 1 was 0.03 μg/ml.

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References and Notes

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4. After the submission of this manuscript a report concerning full structures of punaglandins appeared, see: B.J.Baker, R.K.Okuda, P.T.K.Yu, and P.J.Scheuer, J. Am. Chem. Soc., 107, 2976 (1985). The compound 1 corresponds to 6-epi-14,15-dihydropunaglandin 4.
5. The compound 2 was easily prepared from 1,5-pentanediol by four steps, i) 1 equiv of benzyl bromide, 1 equiv of NaH, THF-DMF, -25°C; ii) PCC, 3Å molecular sieves, CH_2Cl_2, 25°C; iii) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 25°C; iv) diisobutylaluminium hydride, CH_2Cl_2-hexane, -78°C.
6. All new compounds have been fully characterized by IR, ^{1}H-NMR (200 MHz or 400 MHz), and high resolution mass spectroscopy and/or combustion analysis.
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8. K.Ogura, M.Yamashita, and G.Tsuchihashi, Tetrahedron Lett., 759 (1976).
9. $[\alpha]_D$ -10.8° (c=0.50, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.87 (t, J=7.1 Hz, 3H), 1.36 (s, 3H), 1.49 (s, 3H), 2.58 (d, J=5.3 Hz, 1H), 3.35 (s, 3H), 3.65 (s,3H), 4.07 (t,J=5.3Hz,1H), 4.20 (ddd, J=9.6, 5.8, 3.5 Hz, 1H), 4.45 (dd, J=5.3, 5.8 Hz, 1H), 4.71 (s,2H), 7.6 (s,1H).
10. $[\alpha]_D$ -49.2° (c=0.24, $CHCl_3$); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.86 (t, J=7.1 Hz, 3H), 2.08 (s, 3H), 2.10 (s, 3H), 3.64 (s, 3H), 5.06 (m, 1H), 6.20 (dd, J=9.6, 2.5 Hz, 1H), 6.52 (dd, J=9.6, 0.5 Hz, 1H), 7.30 (d, J=0.5 Hz, 1H).
11. During this process, the carbomethoxy group was partly hydrolyzed, therefore the reesterification process was required for obtaining an increased yield.

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