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DENSELY FUNCTIONALIZED CYCLOPENTENONES

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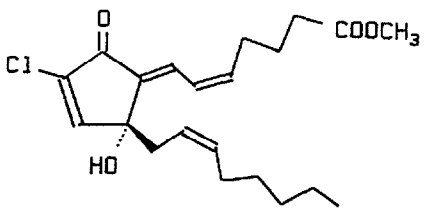
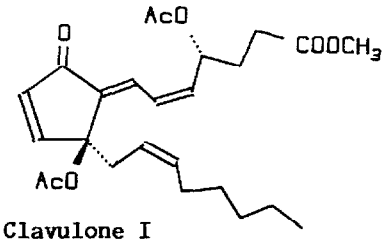
Summary: The cationic cyclopentannelation reaction tolerates alkyl substitution both on the allene ether fragment as well as on the terminus of the enone fragment. The densely functionalized cyclopentenone products are models for a marine prostanoid synthesis.

Prostanoids were discovered in marine organisms[2] not long after their presence was identified in mammalian tissues. More recently, a series of marine prostanoids, some bearing a vinyl halogen in the five-membered ring and/or multiple acetoxy groups, have been isolated and the structures identified. Clavulones and chlorovulones, inter alia, have been isolated from the stolonifer Clavularia viridis,[3] whereas the punaglandins have been found in the Hawaiian octocoral Telesto riisei.[4] Both the punaglandins and the chlorovulones have shown exceptional antiproliferative activity in HL-60 and HeLa cells.[3c,5] The unusual chemical structures and the extraordinary cytotoxicity of these compounds have attracted the interest of synthetic chemists.[4b,6] A method for the rapid assembly of densely functionalized cyclopentenones which was discovered in our labs appeared to offer a useful entry into this class of compounds.[7]



Chlorovulone I



Clavulone I

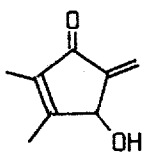
In order to explore the utility of the cationic cylopentannelation for the chemical synthesis of marine prostanoids, hydroxycyclopentenone **1**[8] was first treated with 3 equiv of methyllithium in ether/THF at -78° C to produce diol **2** in 80% yield. Diol **2** was somewhat sensitive to acid, therefore it was oxidized with active manganese dioxide[9] to produce hydroxydienone **3a** in 83% yield. Hydroxydienone **3a** incorporates the **exo**-double bond, the tertiary alcohol and the cyclopentenone functionality which is present in the natural products. The next task was to devise a more convergent approach to **3**. Following the logic set forth in earlier work,[7] it appeared that the cyclization of **4** might offer an advantage over the longer route proceeding from **1**. Substrate **4**, however, appeared to be an unsuitable candidate for the cyclization reaction: substrates for the cationic cyclization which incorporate a Z-alkene had not undergone the cyclization reaction. Notwithstanding, vinylogous trimethylsilyl ester **5**

was prepared from commercially available 3-methyl-2,4-pentanedione by treatment in CH_2Cl_2 with 1.6 equiv of triethylamine and 1.3 equiv of trimethylsilyl trifluoromethanesulfonate. Without purification, crude **5** was exposed to 3 equiv of the lithio anion of (methoxy)methoxyallene in ether/THF at -78° C. Quenching the reaction with aqueous sodium bicarbonate, ether extraction and purification by flash chromatography (4/1, hexanes/EtOAc) produced **4** as a 1/1 mixture of **E** and **Z** isomers in 60% yield. The cyclization of **4** was accomplished according to the optimized conditions which had been developed in previous work.[7] Thus, sequential exposure of a 0.05 M solution of **4** in dry dichloromethane at -30° C to 6 equiv of 2,6-lutidine followed by 5 equiv of trifluoroacetic anhydride gave, after aqueous bicarbonate quench, workup and flash column chromatography (30/1, hexanes/EtOAc) cyclopentenone **3b** in 83% yield. It is noteworthy that the trimethylsilyl ether is retained in the cyclization product. This satisfying result demonstrated that the scope of the cyclopentannelation reaction was not limited to substrates bearing a monosubstituted **E**-alkene.[10]

Cyclopentenone **3b** was treated in ether solution at -78° C with the higher-order cuprate derived from 3 equiv of n-butyllithium and 1.5 equiv of cuprous cyanide. Quenching of the reaction mixture with 4 equiv[11] of phenylselenenyl bromide, followed by warming to 25° C, workup and purification (flash chromatography, 10/1, hexanes/CH_2Cl_2) produced alpha-phenylselenocyclopentenone **6** as a 4/1 mixture of diastereomers in 82% yield. Oxidative deselenation with aqueous hydrogen peroxide in CH_2Cl_2 provided, after purification, 70% of **7** as a *ca.* 1/1 mixture of **E** and **Z** geometric isomers.[12]

Having demonstrated that an "upper sidechain" could be introduced by using a conjugate addition-selenation-elimination strategy, an even more highly convergent synthesis of **7** was undertaken. For this exercise, a substituted (methoxy)methoxyallene was needed. Accordingly, the lithio anion of (methoxy)methoxyallene was quenched with trimethylsilyl chloride to produce allene **8**.[13] Deprotonation of **8** with t-butyllithium took place at the distal carbon; trapping with 1-bromobutane produced **9a**, which was desilylated to **9b** by treatment with tetra-n-butylammonium fluoride (overall yield 38%). The deprotonation of **9b** with n-butyllithium produced a lithioallene which was allowed to react with **5**. Tertiary alcohol **10**, the reaction product, was isolated in 62% yield as a mixture of diastereoisomers. The cyclization of **10** with 2,6-lutidine and trifluoroacetic anhydride produced **7** in 70% yield, again as a *ca.* 1/1 mixture of **E** and **Z** geometric isomers.

These results substantially broaden the scope of the cationic cyclopentannelation reaction by demonstrating, (1) that substitution at the terminus of the vinylogous ester is tolerated by the reaction, and that a tertiary alcohol group can be formed on the five-membered ring, and (2) that substitution on the allene is also tolerated. Taken together, these results suggest a highly convergent methodology for the synthesis of marine prostanoids and related compounds. Two problems remain: the control of the geometry of the exocyclic double bond and the induction of asymmetry during the



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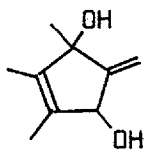

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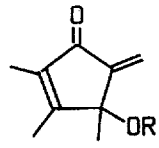
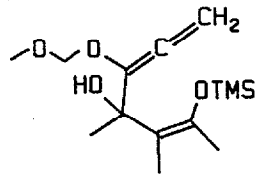


3a R=H
3b R=TMS



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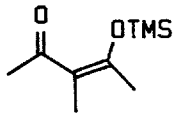

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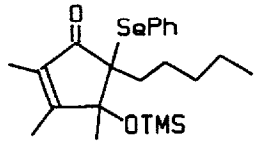

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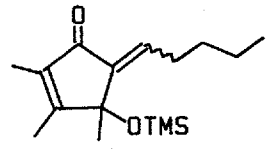

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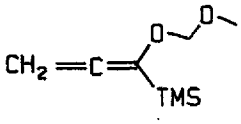

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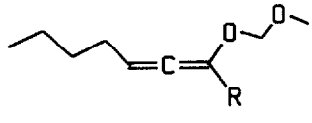
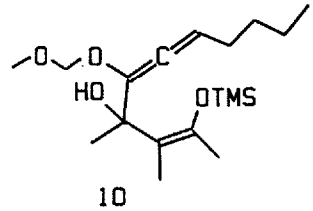


9a R=TMS
9b R=H



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cyclization reaction.

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11. Some of the phenylselenenyl bromide was scavenged by CuCN to form PhSeCN.
12. **7**, Z isomer: ^{1}HNMR (300 MHz, $CDCl_3$) 6.14 (t, J=7.6 Hz, 1 H), 2.89-2.72 (m, 2 H), 1.95 (s, 3H), 1.72 (s, 3 H), 1.47-1.35 (m, 4 H), 1.38 (s, 3 H), 0.92 (t, J=7.2 Hz, 3 H), -0.036 (s, 9 H) ppm; ^{13}CNMR (75 MHz, $CDCl_3$) 195.48, 165.04, 140.04, 139.29, 138.42, 78.30, 31.30, 27.46, 26.91, 22.57, 13.89, 10.89, 7.91, 1.74 ppm; ir (neat) 2980, 1690, 1640, 1650 cm^{-1}; mass spectrum m/e 280 (M^+, 99%), 265, 251, 237, 223, 209, 190, 175, 161, 148, 135, 119, 105; calcd for $C_{16}H_{28}O_2Si$ 280.1851, found 280.1848; calcd for fragment $C_{14}H_{23}O_2Si$ 251.1461, found 251.1482.
7, E isomer: ^{1}HNMR (300 MHz, $CDCl_3$) 6.52 (t, J=7.8 Hz, 1 H), 2.54-2.32 (m, 2 H), 1.98 (s, 3 H), 1.76 (s, 3 H), 1.46 (s, 3 H), 1.51-1.41 (m, 4 H), 0.94 (t, J=7.0 Hz, 3 H), -0.047 (s, 9 H) ppm; ^{13}CNMR (75 MHz, $CDCl_3$) 194.30, 167.18, 140.12, 137.43, 135.78, 78.21, 30.89, 28.06, 26.20, 22.70, 13.95, 10.89, 8.21, 1.47 ppm; ir (neat) 2980, 1700, 1670, 1640 cm^{-1}; mass spectrum m/e 280 (M^+, 9%), 265 (100%), 209, 190, 175, 161, 148, 135, 105; calcd for $C_{16}H_{28}O_2Si$ 280.1851, found 280.1849; calcd for fragment $C_{15}H_{25}O_2Si$ 265.1617, found 265.1668.
13. The substituted allenes were first prepared by Jean M. Cullingham in these laboratories (M. A. Tius and J. M. Cullingham, unpublished results).

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