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A Vinylogous Urethane Approach Towards the Synthesis of Okadaic Acid. Construction of the C1–C8 Fragment. Part I#.

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Abstract: A vinylogous urethane approach is utilized to synthesize the C1-C8 fragment of okadaic acid. The key steps include an asymmetric alkylation, a hydroxyl directed iodocarbonate cyclization and a stereoselective cyanohydrin formation.

Okadaic acid (**1**) is a cytotoxic ionophore isolated from the black marine sponges *Halichondria okadai* and *Halichondria melanodocia*.[1] Most of the biological activity of okadaic acid stems from the fact that it is a potent inhibitor of serine/threonine protein phosphatases 1 (PP1) and 2A (PP2A).[2,3] Thus, okadaic acid is used as a powerful probe for the investigation of the role of protein phosphatases and of PP1/PP2A mediated events. To date, there have been two total syntheses of okadaic acid.[4]

In our approach towards the synthesis of okadaic acid, four segments were prepared corresponding to C1-8 (**2**), C9-18 (**3**) C19-27 (**4**) and C28-38 (**5**) (Figure 1). The synthesis of aldehyde (**2**) will be discussed in this paper with the syntheses of the remaining segments disclosed in the following three papers.

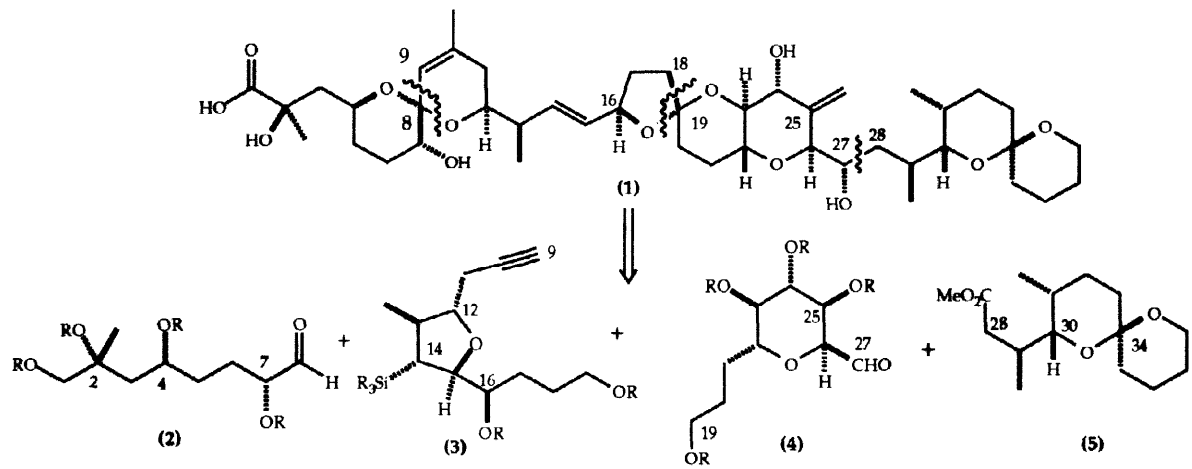

Figure 1

Aldehyde (**2**) represents C1-C8 of okadaic acid. The key steps of this synthesis revolve around the installation of the three stereocenters, including a quaternary center at C-2. Each of these centers is set by the

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initial enantioselective alkylation (C-4) of a vinylogous urethane lactone (VUL) enolate, including the remote stereocenter at C-7.

Alkylation of the enolate derived from vinylogous urethane lactone (**6**) with methallyl bromide afforded vinylogous urethane lactone (**7**)[5] in excellent yield.[6] Reduction of vinylogous urethane lactone (**7**) provided a single β-aminolactone (such that the chiral auxiliary and the methallyl group are on the same face), which upon Cope elimination, furnished the desired α,β-unsaturated lactone (**8**) with high enantiomeric purity (97% *ee*) (Figure 3).[7]

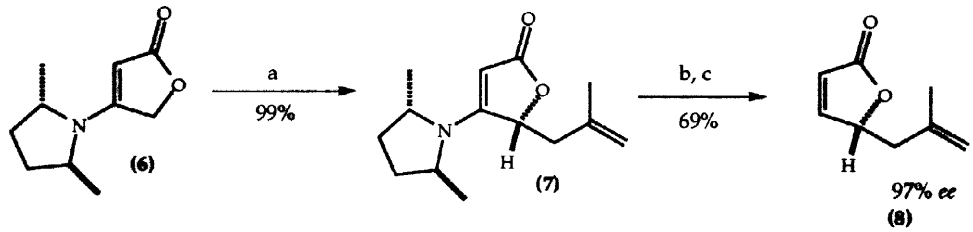

Figure 2: (a) t-BuLi, THF, -78°C; methallyl bromide (b) $NaCNBH_3$, HOAc (75%) (c) *m*-CPBA, CH_2Cl_2, 0°C; *aq.* $NaHCO_3$ (92%)

α,β-Unsaturated lactone (**8**) was then selectively reduced using $NaBH_4/CuCl_2{\cdot}2H_2O$ to provide saturated lactone (**9**).[8] Other transition metal salts such as $CoCl_2{\cdot}6H_2O$ and $NiCl_2{\cdot}6H_2O$ caused concomitant reduction of the double bond at C-1/C-2. Since the alcohol functionality at C-4 is needed to direct the formation of the tertiary alcohol at C-2, lactone (**9**) was reduced to the diol which was selectively protected to provide the primary *t*-butyldiphenylsilyl ether (**10**) (Figure 3).

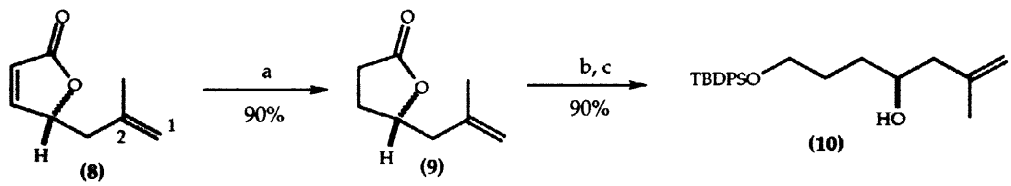

Figure 3: (a) $NaBH_4$, $CuCl_2{\cdot}2H_2O$, MeOH, 0°C (b) LAH, THF, 0°C (92%) (c) TBDPSCl, imidazole, CH_2Cl_2, 0°C (98%)

It has been shown that iodocarbonate formation through the corresponding allylic alcohol gives the *cis*-carbonate.[9] However, attempts to form the iodocarbonate (**12**) directly from the homoallylic alcohol (**10**) provided the desired product in low yield. The yield of (**12**) could be substantially increased by initial formation of *t*-butylcarbonate (**11**) followed by treatment with iodine (Figure 4).

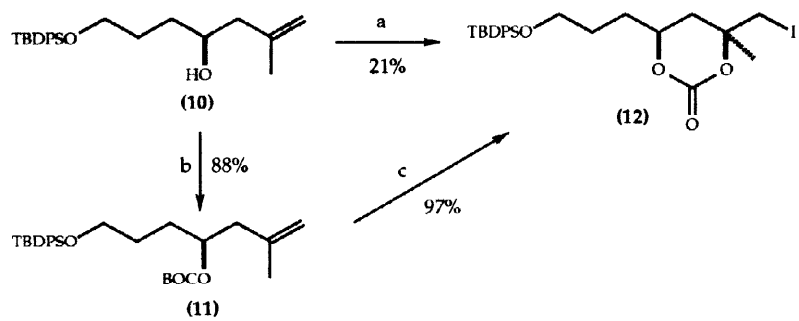

Figure 4: (a) *n*-BuLi, THF; CO_2; I_2, THF (b) *n*-BuLi, THF; BOC-ON (c) I_2, EtCN, -40°C

At this stage it was necessary to invert the tertiary alcohol center at C-2. It had been previously reported that treatment of an iodocarbonate with aqueous potassium hydroxide furnished a β-hydroxy epoxide which upon treatment with a catalytic amount of acid and water provided a triol where the tertiary center has been inverted.[9a,10] Thus, treatment of the iodocarbonate (12) with aqueous potassium carbonate yielded β-hydroxy epoxide (13). In order to install the remote stereocenter at C-7 it is necessary to protect the secondary alcohol to prevent lactol formation. Therefore, the secondary alcohol was protected as an allyl ether. Acid catalyzed ring opening of the epoxide, in the presence of acetone formed acetonide (14) *in situ*. The optimal conditions for removal of the silyl ether from (14) was accomplished under basic conditions to provide the desired alcohol which was then oxidized under Swern conditions. This aldehyde was then converted to its bis-benzyl acetal (15) (Figure 5).

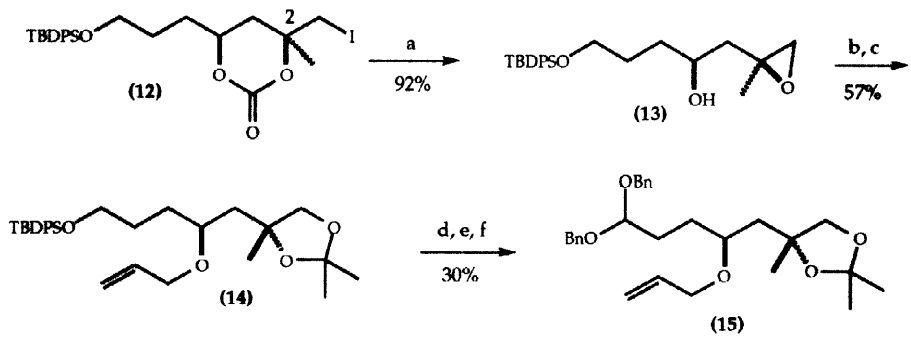

Figure 5: (a) *aq.* KOH/DME (b) KH, DME, TBAI, allyl bromide, 0°C (84%) (c) H_2SO_4, acetone (68%) (d) NaH, DMF (64%) (e) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78°C - 0°C (75%) (f) BnOTMS, TMSOTf, CH_2Cl_2, -78°C (62%)

At this point the final stereocenter at C-7 was incorporated. This would involve a homologation by one carbon to afford the desired aldehyde (17). Molander has recently shown that 1,4-asymmetric induction can be achieved by the addition of trimethylsilylcyanide to acetals.[11] This is postulated to proceed through a cyclic onium species, which requires a bulky acetal substituent in order to prevent equilibration of the two "anomeric" forms as well as an electron rich ether to enable the cyclic species to form. Therefore, treatment of bis-benzylacetal (15) with trimethylsilylcyanide, at -45°C provided cyanohydrin (16) which was subsequently reduced with DIBAL to provide the requisite aldehyde (17) in modest and unoptimized yield (Figure 6).

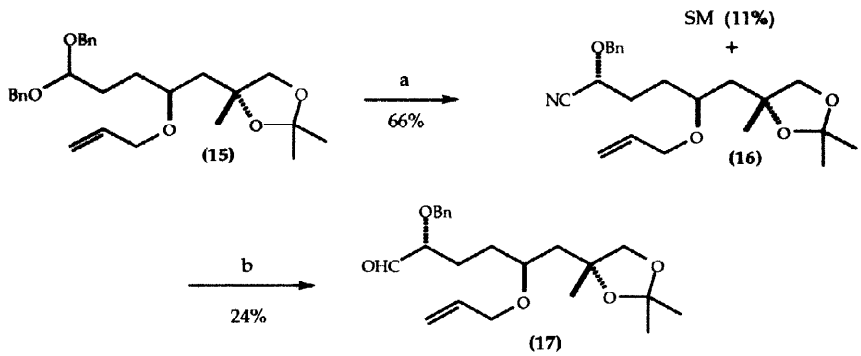

Figure 6: (a) TMSCN, CH_2Cl_2, cat. TMSOTf, -45°C (b) DIBAL, hexanes, THF; SiO_2, H_2O, Et_2O

In conclusion, aldehyde (**17**) was prepared in 16 steps with an overall yield of 1.2% which represents an average yield of 79% for each step. This approach towards okadaic acid exemplifies the utility of the vinylogous urethane lactone in alkylation reaction with an activated alkyl halide. The stereochemistry imparted by the *trans* 2,5-dimethyl pyrrolidine chiral auxiliary not only sets this stereocenter, but indirectly the quaternary center through a diastereoselective iodocarbonate formation as well as the remote center at C-7 by incorporation of a cyanohydrin providing a *trans* 1,4-dialkoxy stereochemical relationship.

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Dedicated to the memory of Professor Richard H. Schlessinger

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