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A Vinylogous Urethane Approach Towards the Synthesis of Okadaic Acid. Construction of the C9–C18 Fragment. Part II#.

Sharon M. Dankwardt*‡, John W. Dankwardt‡, and Richard H. Schlessinger

University of Rochester, Department of Chemistry

Rochester, NY 14627

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Abstract: A diastereo- and enantioselective acylation-reduction sequence of a vinylogous urethane lactone silylketene acetal sets the initial stereocenter in this approach towards the C9-C18 fragment of okadaic acid. The remainder of the stereocenters are installed *via* a silyl cuprate conjugate addition trapping sequence, and a lactol is transformed to a tetrahydrofuran by addition of a propargyl aluminum species. A novel tetrahydrofuran ring opening reaction utilizing dimethyl boron bromide is also illustrated.

Okadaic acid (**1**) is a marine natural product[1] which has been shown to be a useful biological probe due to its ability to inhibit serine/threonine protein phosphatases 1 (PP1) and 2A (PP2A).[2,3] To date, there have been two total syntheses of okadaic acid.[4] This paper illustrates the synthesis of the C9-C18 portion of the natural product.

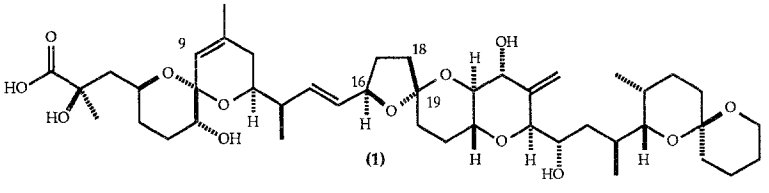

Figure 1

Tetrahydrofuran (**2**) represents C9-C18 of okadaic acid. The initial stereocenters to be installed will be at C15 and C16. These will be set in an enantio- and diastereoselective manner by an acylation-reduction sequence using a chiral vinylogous urethane lactone silylketene acetal. The stereocenter at C14 is not utilized in the natural product but is used to establish the center at C13 through a conjugate addition of a silyl cuprate followed by trapping with methyl iodide as well as the olefin geometry at C14-C15. The final stereocenter is incorporated through addition of a propargyl aluminum species to an cyclic oxonium ion. The double bond at C14-C15 of the natural product will be incorporated through a novel ring opening reaction of the β-silyl tetrahydrofuran.

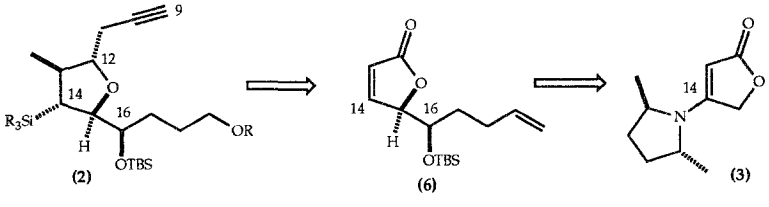

Figure 2

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Deprotonation of the vinylogous urethane lactone (**3**) with *t*-butyllithium followed by treatment with trimethylsilyl chloride gave the intermediate silyl ketene acetal,[5] which upon treatment with 4-pentenoyl chloride afforded the desired ketone. Reduction of the ketone was then accomplished with $Na(OAc)_3BH$[6] to provide alcohol (**4**) which was then protected as its *tert*-butyldimethylsilyl ether (**5**) (Figure 3). The use of a bulky pyridine base was necessary to prevent β-elimination. The diastereoselectivity of the reduction of the intermediate ketone can be explained invoking a Felkin-Anh model.[7]

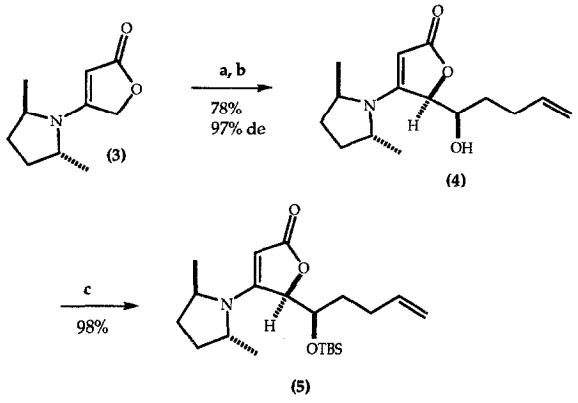


Figure 3: (a) *t*-BuLi, THF; TMSCl; 4-pentenoyl chloride (86%) (b) $Na(OAc)_3BH$, $CeCl_3$, MeOH (91%), (c) TBSOTf, 2,6-di-*t*-butylpyridine, CH_2Cl_2 (98%)

Having synthesized vinylogous urethane lactone (**5**), which has the desired *syn* stereochemistry at C15-C16, removal of the chiral auxiliary was necessary to provide unsaturated lactone (**6**). It had been shown previously that $NaCNBH_3$ in acidic THF would reduce the six-membered vinylogous urethane lactones;[8] however, this reaction did not work well in the case of the five-membered lactones. By changing the solvent to glacial acetic acid we were able to use $NaCNBH_3$ to convert vinylogous urethane lactone (**5**) to a single β-aminolactone, where the chiral auxiliary and the side chain are on the same face of the lactone. Oxidation of the tertiary amine of the lactone with *m*-CPBA followed by aqueous $NaHCO_3$ provided α,β-unsaturated lactone (**6**) (Figure 4).

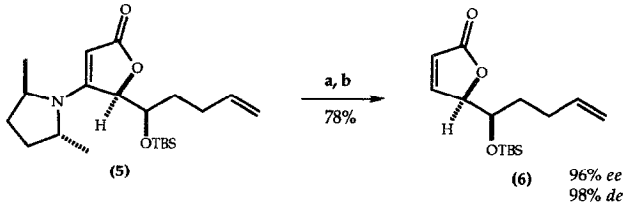


Figure 4: (a) $NaCNBH_3$, HOAc (92%) (b) *m*-CPBA, CH_2Cl_2; *aq.* $NaHCO_3$ (85%)

Conjugate addition of dimethylphenylsilyl cuprate[9] to lactone (**6**) followed by alkylation with methyl iodide provided the desired β-silyl lactone (**7**) (Figure 5). Assignment of the stereochemistry in (**7**) is supported by the large coupling constants observed for the protons on the butanolide, $J_{13,14} = 11.58$ Hz, $J_{14,15} = 9.69$ Hz in the ^1H NMR spectrum of (**7**).

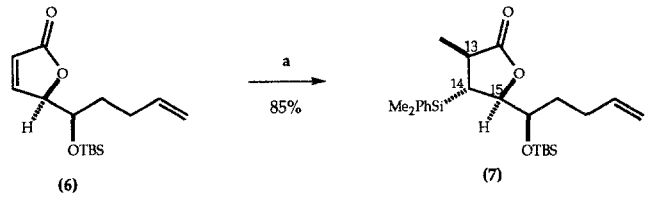


Figure 5: (a) $Me_2PhSiLi$, CuCN, THF, 0°C; (**6**), -20·C; MeI, -20°C - RT (85%)

Ozonolysis of olefin (**7**) provided the aldehyde which was then reduced to the corresponding primary alcohol. The alcohol was then protected with triethylsilyl chloride to afford ether (**8**) (Figure 6).

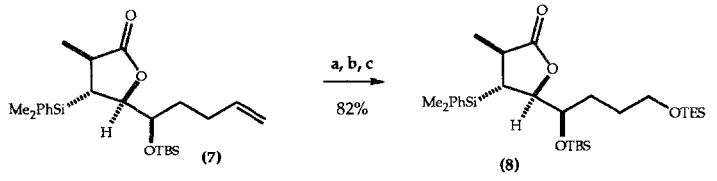


Figure 6: (a) O_3, CH_2Cl_2, -78°C; Ph_3P, -78°C - RT (92%) (b) $NaBH_4$, EtOH, H_2O, 0°C (97%) (c) TESCl, imidazole, DMAP, CH_2Cl_2, 0°C (92%)

At this point we decided to incorporate the propargyl unit at C-12. Towards this end, lactone (**8**) was reduced to its lactol and was converted into the acetate (**9**). Acetate (**9**) was then treated with $ZnCl_2$•Et_2O followed by addition of the propargyl aluminum reagent to afford the desired tetrahydrofuran (**10**) as a single diastereomer (Figure 7). Thus, tetrahydrofuran (**10**) was prepared in twelve steps with an overall yield of 15%.

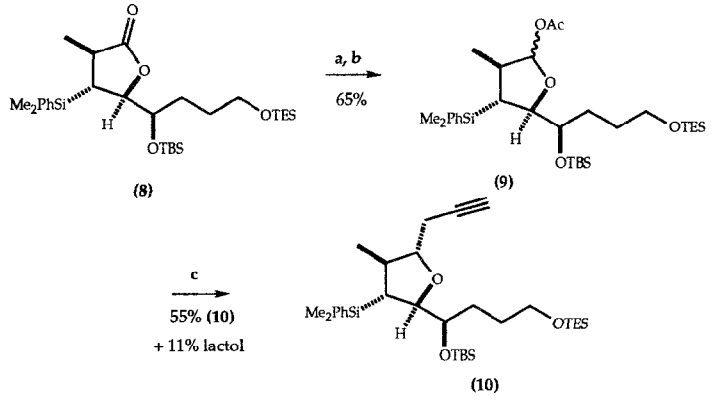
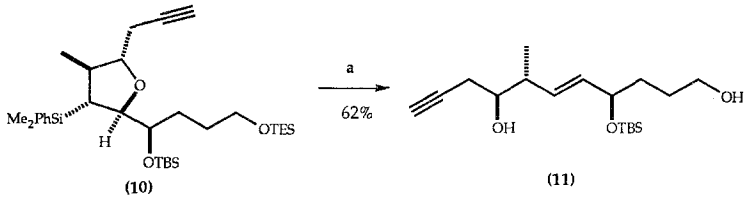


Figure 7: (a) DIBAL, toluene, -78°C (99%) (b) Ac_2O, pyridine, DMAP, CH_2Cl_2 (66%) (c) $ZnCl_2$•Et_2O, CII_2Cl_2, -78°C; Al, $HgCl_2$, THF, propargyl bromide (55% (**10**) and 11% lactol)

With the tetrahydrofuran (**10**) in hand, we needed to test the feasibility of opening the tetrahydrofuran ring to give the desired olefinic alcohol (**11**). After extensive experimentation, dimethylboron bromide[10] proved to be the only reagent which provided any of the desired olefinic alcohol (**11**) (Figure 8). The dimethylboron

bromide presumably complexes with the oxygen of the tetrahydrofuran ring. Attack of a nucleophile assists in breaking the carbon-silicon bond in what is similar to an acid catalyzed Peterson olefination reaction.[11]



(10) (11)

Figure 8: (a) Me_2BBr, Et_3N, CH_2Cl_2, -78°C (62%)

In conclusion, this approach demonstrates use of vinylogous urethane lactone in diastereo- and enantioselective acylation-reduction reactions to provide a *syn* stereochemical relationship between C15-C16. An effective use of a stereochemical relay is utilized to incorporate the remaining stereocenters. A unique tetrahydrofuran ring opening reaction is also illustrated as a new technique to incorporate the olefin moiety into okadaic acid.

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REFERENCES AND NOTES

Dedicated to the memory of Professor Richard H. Schlessinger.

‡ Current address: Roche Bioscience, 3401 Hillview Ave, Palo Alto, CA 94304

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