

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

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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. © 1998 Elsevier Science Ltd. All rights reserved.

Okadaic acid (**1**) is a marine natural product<sup>1</sup> 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),<sup>2,3</sup> To date, there have been two total syntheses of okadaic acid.<sup>4</sup> This paper illustrates the synthesis of the C9–C18 portion of the natural product.

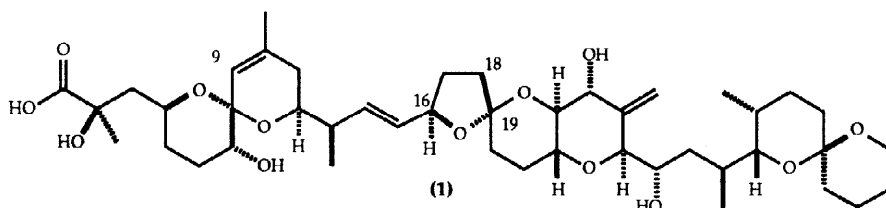


Figure 1

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  $\beta$ -silyl tetrahydrofuran.

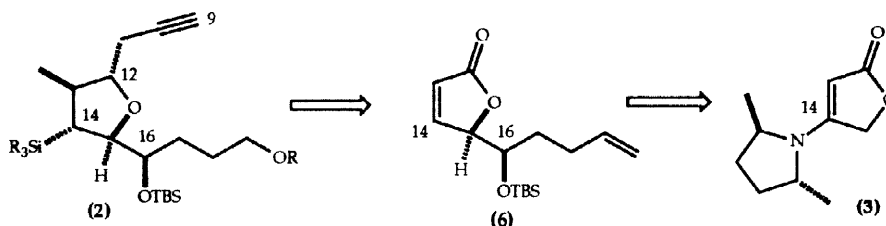


Figure 2

Deprotonation of the vinylogous urethane lactone (**3**) with *t*-butyllithium followed by treatment with trimethylsilyl chloride gave the intermediate silyl ketene acetal,<sup>5</sup> which upon treatment with 4-pentenoyl chloride afforded the desired ketone. Reduction of the ketone was then accomplished with Na(OAc)<sub>3</sub>BH<sup>6</sup> 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  $\beta$ -elimination. The diastereoselectivity of the reduction of the intermediate ketone can be explained invoking a Felkin-Anh model.<sup>7</sup>

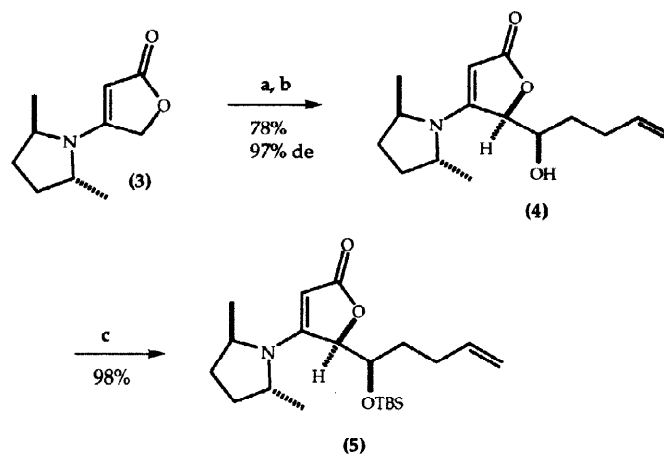


Figure 3: (a) *t*-BuLi, THF; TMSCl; 4-pentenoyl chloride (86%) (b) Na(OAc)<sub>3</sub>BH, CeCl<sub>3</sub>, MeOH (91%), (c) TBSOTf, 2,6-di-*t*-butylpyridine, CH<sub>2</sub>Cl<sub>2</sub> (98%)

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<sub>3</sub> in acidic THF would reduce the six-membered vinylogous urethane lactones;<sup>8</sup> 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<sub>3</sub> to convert vinylogous urethane lactone (**5**) to a single  $\beta$ -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<sub>3</sub> provided  $\alpha,\beta$ -unsaturated lactone (**6**) (Figure 4).

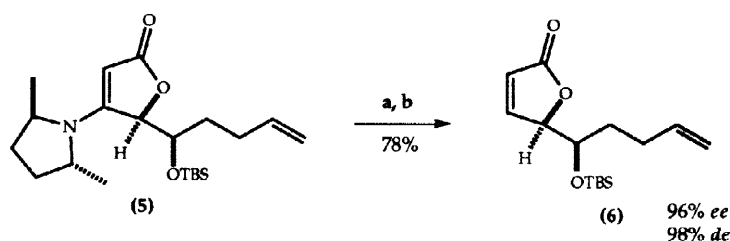


Figure 4: (a) NaCNBH<sub>3</sub>, HOAc (92%) (b) *m*-CPBA, CH<sub>2</sub>Cl<sub>2</sub>; aq. NaHCO<sub>3</sub> (85%)

Conjugate addition of dimethylphenylsilyl cuprate<sup>9</sup> to lactone (**6**) followed by alkylation with methyl iodide provided the desired  $\beta$ -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 <sup>1</sup>H NMR spectrum of (**7**).

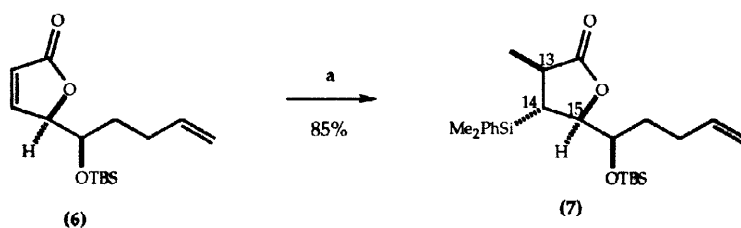


Figure 5: (a)  $\text{Me}_2\text{PhSiLi}$ ,  $\text{CuCN}$ , THF,  $0^\circ\text{C}$ ; (6),  $-20^\circ\text{C}$ ;  $\text{MeI}$ ,  $-20^\circ\text{C}$  - RT (85%)

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).

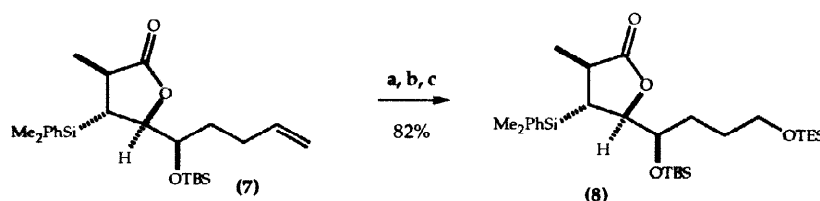


Figure 6: (a)  $\text{O}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ;  $\text{Ph}_3\text{P}$ ,  $-78^\circ\text{C}$  - RT (92%) (b)  $\text{NaBH}_4$ , EtOH,  $\text{H}_2\text{O}$ ,  $0^\circ\text{C}$  (97%) (c)  $\text{TESCl}$ , imidazole, DMAP,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  (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  $\text{ZnCl}_2 \cdot \text{Et}_2\text{O}$  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%.

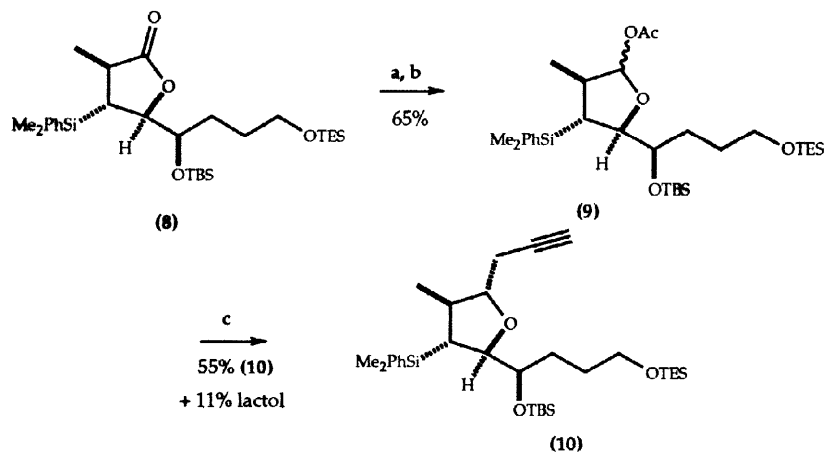


Figure 7: (a) DIBAL, toluene,  $-78^\circ\text{C}$  (99%) (b)  $\text{Ac}_2\text{O}$ , pyridine, DMAP,  $\text{CH}_2\text{Cl}_2$  (66%) (c)  $\text{ZnCl}_2 \cdot \text{Et}_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ;  $\text{Al}$ ,  $\text{HgCl}_2$ , THF, propargyl bromide (55% (10) 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<sup>10</sup> 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.<sup>11</sup>

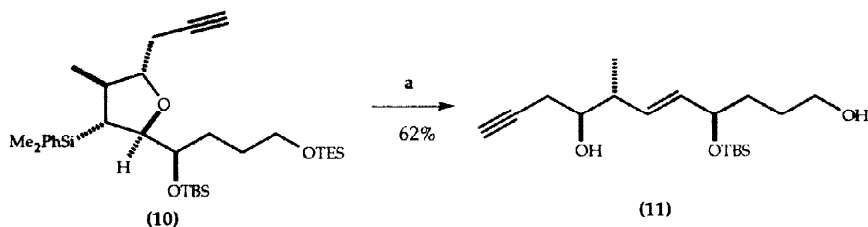


Figure 8: (a) Me<sub>2</sub>BBr, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -78°C (62%)

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.  
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