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LETTERS

# Synthesis of the C28 Through C38 Segment of Okadaic Acid Using Vinylogous Urethane Aldol Chemistry: Part IV[#]

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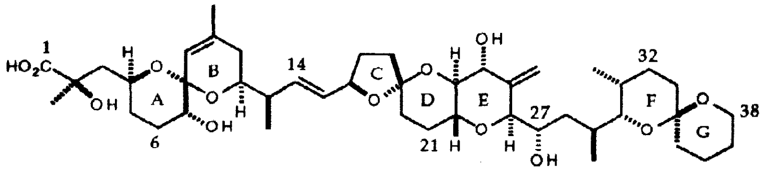
**Abstract:** The synthesis of the C-28 through C-38 segment of the marine natural product okadaic acid was accomplished employing a highly enantio- and diasteroselective aldol condensation reaction of a chiral vinylogous urethane enolate. The stereocenter at C-29 was addressed utilizing a diastereoselective hydroboration reaction. © 1998 Elsevier Science Ltd. All rights reserved.

Okadaic acid **1** is a marine natural product isolated from the *Halichondria okadaia* and *Halichondia melanodocia.*[1] Currently, there are two total syntheses of okadaic acid which, in contrast to our approach, begin with carbohydrate starting materials.[2] Our route to okadaic acid relies on the generation of chirality *via* auxiliary driven enantioselection. The previous three papers described the efficient synthesis of the three segments representing C-1 through C-26 of okadaic acid **1**. The key carbon-carbon bond forming reactions illustrated in these papers employ either a stereoselective aldol, acylation-reduction or alkylation protocol utilizing chiral nonracemic vinylogous urethane (VU) enolates.



okadaic acid, **1**

**Scheme 1**

This paper will provide an account of our recent effort towards the preparation of the spiroketal **19** which embodies C-28 through C-38 of okadaic acid **1**.[3] The *syn-anti* stereochemical triad (C-31 to C-29) will be addressed by incorporating two stereochemical determining reactions. An enantioselective *syn* aldol condensation using a chiral pyrrolidine auxiliary will establish the C-30/C-31 stereocenters while a diastereoselective hydroboration will configure the third chiral center at C-29.

Recent studies from the Schlessinger group have described the application of VU enolates in *syn* selective aldol condensation reactions.[4] Application of this technology will provide a facile entry into the spiroketal fragment **19** (C-28 to C-38) of okadaic acid. Condensation of the VU enolate, prepared from **2** and LDA, with methacrolein provided the *syn* vinylogous urethane lactone (VUL) **3** with high levels of enantio- and diastereoselectivity.

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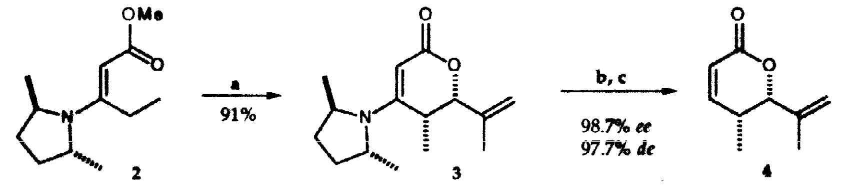
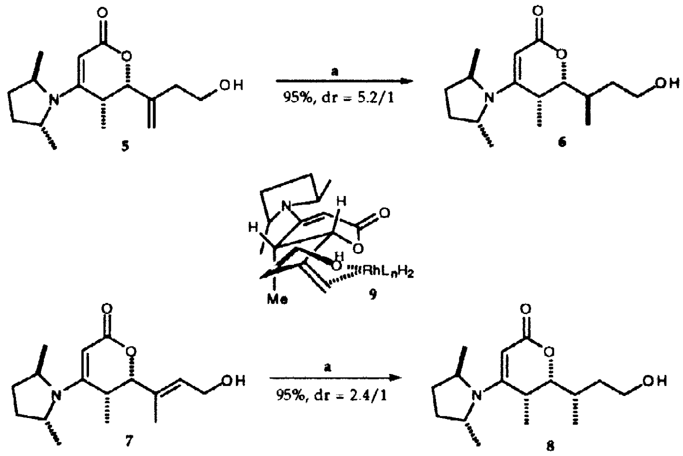


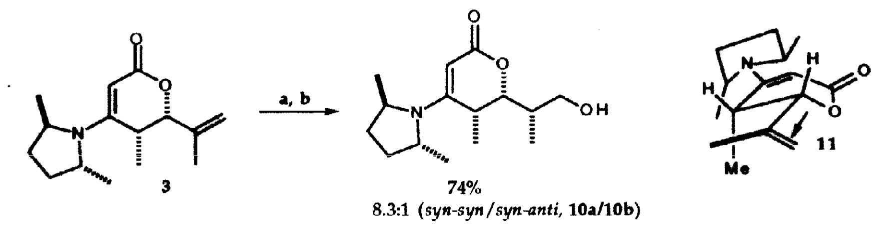
**Scheme 2:** (a) (1) LDA, THF, 0°C (2) methacrolein (b) $NaCNBH_3$, HCl, THF (c) $CH_3CO_2H$, Δ

The chiral auxiliary could be removed by reduction of **3** to the β-aminolactone followed by a facile acid-mediated elimination to afford the lactone **4**.[5] The enantioselectivity was determined to be > 98% by chiral HPLC techniques. In our initial strategy, it was decided to install the stereocenter at C-29 by hydrogenation of either the homoallylic alcohol **5** or allylic alcohol **7**.[6]



**Scheme 3:** $Rh(1,4\text{-DIPHOS})(NBD)^+BF_4^-$, $CH_2Cl_2$, $H_2$ (650 psi)

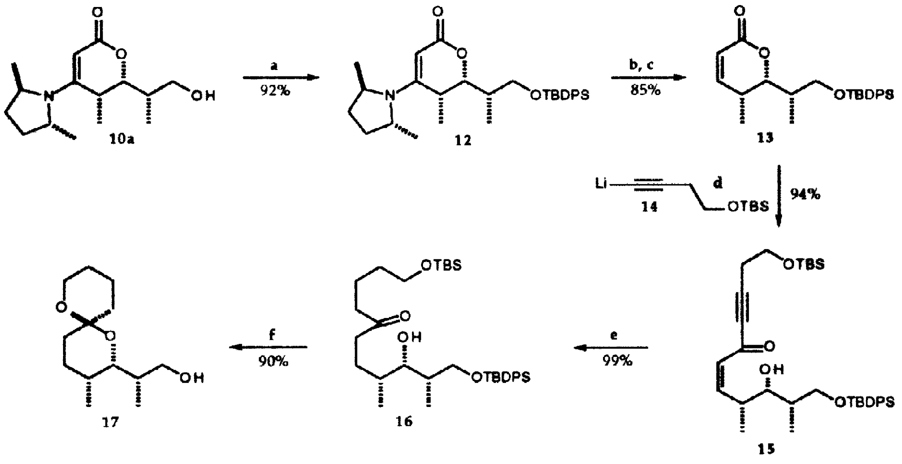
Among the best catalysts surveyed was the cationic rhodium complex ($Rh(1,4\text{-DIPHOS})(NBD)^+BF_4^-$) which afforded the highest levels of diastereoselectivity.[7,8] The structure of the major isomer was determined by X-ray analysis to be the *syn-anti* vinylogous urethane lactone **6**.[9] The allylic alcohol **7** was also submitted to the hydrogenation conditions, again using $Rh(1,4\text{-DIPHOS})(NBD)^+BF_4^-$ resulting in moderate levels of selectivity favoring the desired *syn-syn* VU lactone **8**. The selectivity of the hydrogenation of VUL **5** is in accord with hydroxyl coordination to the rhodium catalyst in a conformation in which the olefin is synplanar with respect to the adjacent carbon-oxygen bond of the lactone ring. Delivery of the Rh bound hydrogen will occur from the π-face of the olefin *anti* with respect to the psuedo axial methyl group at C-31 (okadaic acid numbering). Disappointed with the stereoselectivity of the hydrogenation result, we decided to incorporate the stereocenter at C-29 *via* a diastereoselective hydroboration.[10] Thus, treatment of VUL **3** with $BH_3$·THF followed by oxidation of the carbon-boron bond using $Me_3NO$ furnished the alcohols **10a** and **10b** as a 8.3/1 ratio. Other hydroborating reagents such as 9-BBN and thexylborane resulted in complete recovery of starting material.



**Scheme 4:** (a) $BH_3$·THF, THF, 0°C (b) $Me_3NO·2H_2O$, diglyme, 120°C

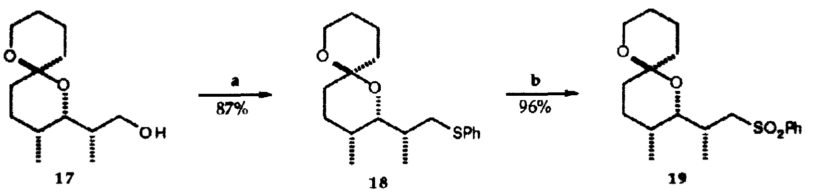
The diastereoselectivity of the hydroboration can be rationalized if one assumes an early transition state for the hydroboration reaction where the ground state conformation and the reactive conformation are similar in structure. As with olefin **5**, the VUL **3** will lie in a *syn*-planar orientation with the carbon-oxygen bond of the lactone ring.[11] The major diastereomer presumably results from approach of the hydroborating reagent from the more accessible π-face of the olefin opposite the psuedo axial methyl group at C-31 as indicated by structure **11**.

The alcohol **10a** was protected as the *tert*-butyldiphenylsilyl ether **12**. The chiral auxiliary was removed as in the previous example to provide the unsaturated lactone **13**. At this juncture, the spiroketal moiety (ring G) was constructed beginning with the addition of the lithium acetylide **14** to the lactone **13** to provide the ketone **15** in high yield.[12]



**Scheme 5:** (a) TBDPSCl, $CH_2Cl_2$, DMAP, imidazole (b) $NaCNBH_3$, THF, HCl (c) $CH_3CO_2H$, Δ
(d) THF, **14**, -40°C (e) $Rh/Al_2O_3$, $Et_2O$, $H_2$ (150 psi) (f) HF, $H_2O$, $CH_3CN$

The hydroxy-ketone **15** was hydrogenated[13] using $Rh/Al_2O_3$ and subsequent spirocyclization by treatment of **16** with aqueous HF provided the ketal **17**.[14] The stereocenter at C-34 is in accord with the anomeric effect.[15] Direct conversion of alcohol **17** to sulfide **18** using N-thiophenylsuccinimide[16] followed by oxidation with *m*-CPBA[17] gave the desired sulfone **19** in 10 steps with a 33% overall yield. Sulfone **19** was identical to the published spectral and physical data reported by Isobe.[2c]



**scheme 6:** (a) N-thiophenylsuccinimide, $Bu_3P$,benzene (b) *m*-CPBA, $CH_2Cl_2$

In conclusion, the synthesis of the C-28 through C-38 segment of okadaic acid, **1** was accomplished employing a highly enantioselective *syn* aldol condensation reaction of a chiral vinylogous urethane enolate. The stereocenter at C-29 was addressed utilizing a diastereoselective hydroboration reaction. The remaining carbon skeleton of **19** was constructed from the lithium acetylide **14** by addition to the lactone **13**.

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## References and Notes

\# Dedicated to the memory of Professor Richard H. Schlessinger

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1 Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Van Engen, D.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. *J. Am. Chem. Soc.* **1981**, *103*, 2469-2471.

2 Total syntheses: (a) Ichikawa, Y.; Isobe, M.; Bai, D.; Goto, T. *Tetrahedron* **1987**, *43*, 4737-4748. (b) Ichikawa, Y.; Isobe, M.; Goto, T. *Tetrahedron* **1987**, *43*, 4749-4758. (c) Ichikawa, Y.; Isobe, M.; Masaki, H.; Kawai, T.; Goto, T. *Tetrahedron* **1987**,*43*, 4759-4766. (d) Isobe, M.; Ichikawa, Y.; Bai, D.; Masaki, H.; Goto, T. *Tetrahedron* **1987**, *43*, 4767-4776. (e) Isobe, M.; Ichikawa, Y.; Funabashi, Y.; Mio, S.; Goto, T. *Tetrahedron* **1986**, *42*, 2863-2872. (f) Urbanek, R. A.; Sabes, S. F.; Forsyth, C. J. *J. Am. Chem. Soc.* **1998**, *120*, 2523-2533. g) Sabes, S. F.; Urbanek, R. A.; Forsyth, C. J. *J. Am. Chem. Soc.* **1998**, *120*, 2534-2542. Model study: (g) Marko, I. E.; Chelle, F. *Tetrahedron Lett.* **1997**, *38*, 2895-2898. (h) Marko, I. E.; Dobbs, A. P.; Scheirmann, V.; Chelle, F.; Bayston, D. J. *Tetrahedron Lett.* **1997**, *38*, 2899-2902.

3 (a) Dankwardt, J. W. Ph.D. Thesis, University of Rochester, **1991**. (b) Dankwardt, S. M. Ph.D. Thesis, University of Rochester, **1992**.

4 For references describing the aldol chemistry of vinylogous urethane enolates, see: (a) Schlessinger, R. H.; Li, Y.-J.; Von Langen, D. J. *J. Org. Chem.* **1996**, *61*, 3226-32267. (b) Schlessinger, R. H.; Li, Y-J. *J. Am. Chem. Soc.* **1996**, *118*, 3301-3302. (c) Schlessinger, R. H.; Iwanowicz, E.J.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 3070-3073.

5 Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897-2904.

6 These lactones were prepared in analogy to **3** by the aldol condensation of the enolate derived from VU **2** and the appropriate aldehyde, see: reference 3(a).

7 For an excellent review on directed homogeneous hydrogenations see: (a) Brown, J. M. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 190-203. (b) Evans, D. A.; Miller, S. J.; Brown, J. M.; Layzell, T. P.; Ramsden, J. A. in the *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A., Ed., Wiley: New York; **1994**, pp. 388-393.

8 Hydrogenation of **5** and **7** with Pd/C afforded approximately 1/1 mixtures of the two diastereomers **6** and **8**.

9 The structure of compounds **5-8** were determined by single crystal X-ray diffraction methods.

10 Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*, Academic Press: New York, **1988**.

11 The conformation of lactone **3** is based upon the X-ray structure obtained for compound **5**.

12 For excellent reviews on the synthesis and chemistry of spiroketals see: (a) Kluge, A. F. *Heterocycles* **1986**, *24*, 1699-1740. (b) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617-1661. For the use of lithium acetylides for the synthesis of spiroketals see: (c) Baker, R.; Brimble, M. A. *J. Chem. Soc. Perkin Trans. I* **1988**, 125-131. (d) Hanessian, S.; Ugolini, A. *Carbohydr. Res.* **1984**, *130*, 261-269.

13 Rylander, P. N. *Hydrogenation Methods*, Academic Press: San Diego, **1990**.

14 Evans, D. A.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 3129-3132.

15 Deslongchamps, P. in *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press: Oxford, **1983**, pp. 4-21.

16 Walker, K. A. H. *Tetrahedron Lett.* **1977**, 4475-4478.

17 Simpkins, N.S. in *Sulfones in Organic Synthesis*, Pergamon Press: Oxford, **1993**, pp. 5-11.