Pergamon

Tetrahedron Letters 39 (1998) 4983–4986

TETRAHEDRON LETTERS

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

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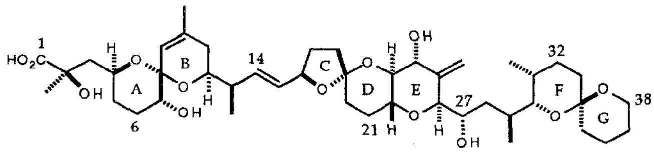
Received 2 April 1998; accepted 4 May 1998

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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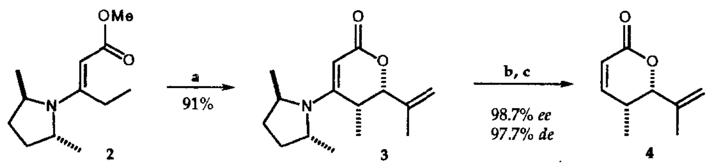
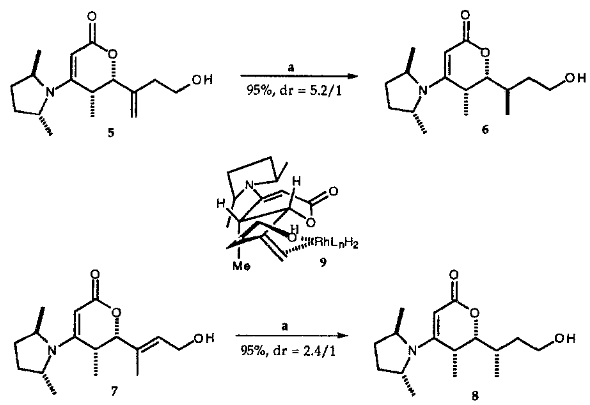
PII: S0040-4039(98)00974-5



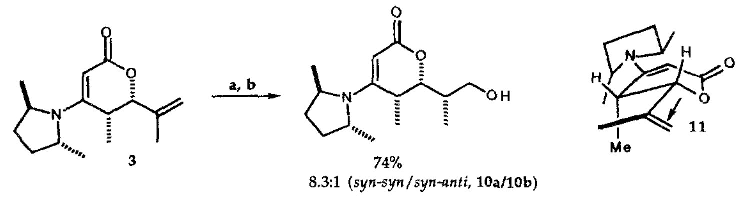
Scheme 2: (a) (1) LDA, THF, 0°C (2) methacrolein (b) $NaCNBH_3$, HCl, THF (c) CH_3CO_2H, Δ

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)

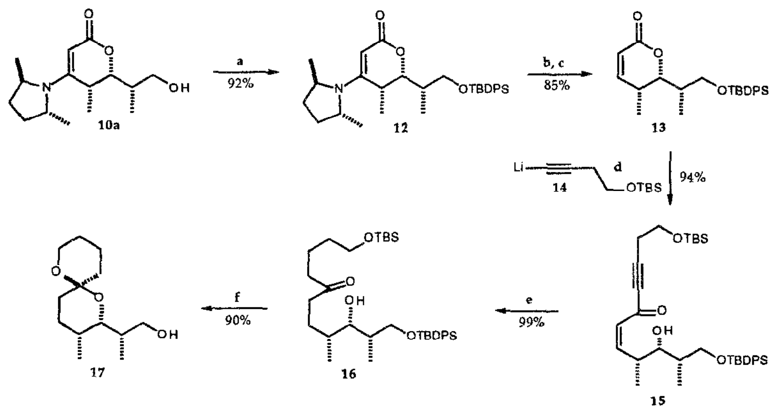
Among the best catalysts surveyed was the cationic rhodium complex ($Rh(1,4\text{-DIPHOS})(NBD)^+BF_4^-$) which afforded the highest levels of diastereoselectivity.[7,8] The structure of the major isomer was determined by X-ray analysis to be the *syn-anti* vinylogous urethane lactone **6**.[9] The allylic 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 $BH_3 \cdot THF$ 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

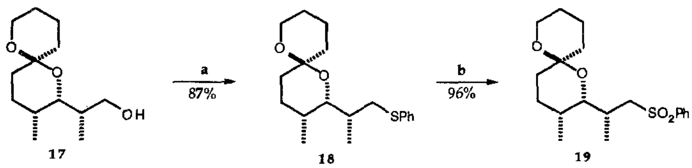
The diastereoselectivity of the hydroboration can be rationalized if one assumes an early transition state for the hydroboration reaction where the ground state conformation and the reactive conformation are similar in structure. As with olefin **5**, the VUL **3** will lie in a *syn*-planar orientation 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**.

Acknowledgments. The X-ray structure analyses were performed by Drs. J. P. Springer and K. Hoogsteen (Merck) and are gratefully acknowledged. Financial support from the NIH, and the following fellowships: Merck Sharp and Dohme, Sherman Clarke and a Lattimore fellowship are gratefully acknowledged.

References and Notes

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

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