



Synthesis of the C19 through C27 Segment of Okadaic Acid Using Vinylogous Urethane Aldol Chemistry: Part III[#]

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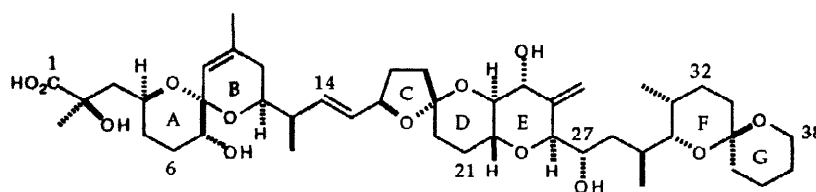
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Received 2 April 1998; accepted 4 May 1998

Abstract: The synthesis of the C-19 through C-27 segment of the marine natural product okadaic acid was accomplished employing a highly enantio- and diastereoselective aldol coupling reaction of a chiral vinylogous urethane lactone enolate. The remainder of the carbon skeleton of this segment was constructed by a diastereoselective γ -oxygenated allylstannane addition. Formation of the tetrahydropyran ring was achieved utilizing a stereoselective electrophilic cyclization.

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Okadaic acid **1**¹ is an ionophore which displays a wide range of biological activity including the ability to inhibit protein phosphatases 1 and 2A of the serine/threonine class.² The previous two papers describe the concise synthesis of the C-1 through C-8 and C-9 through C-18 portions of okadaic acid **1** featuring stereoselective aldol and alkylation chemistry of chiral nonracemic vinylogous urethane enolates.



okadaic acid, **1**

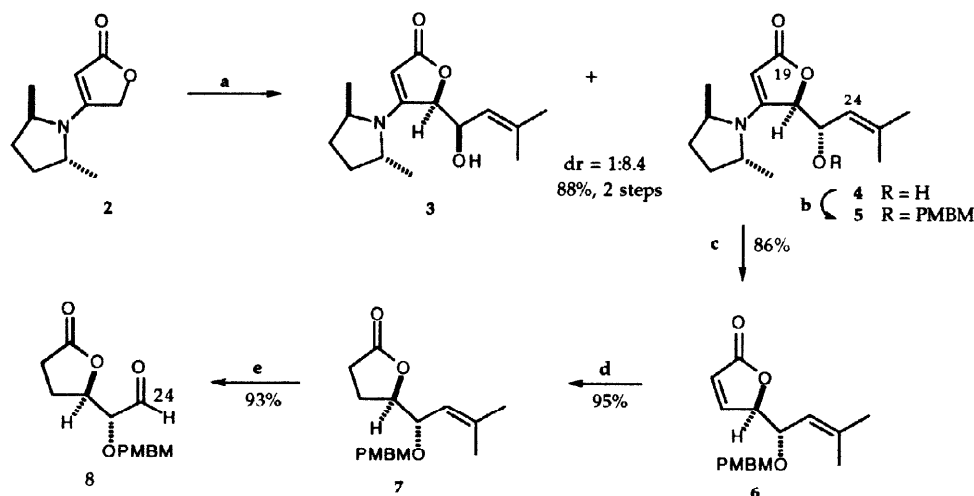
Scheme 1

This paper will provide an account of our effort towards the preparation of **15** which embodies C-19 through C-27 of okadaic acid **1**.³ This section of okadaic acid is composed of a bis-dioxidecalin ring system containing four chiral centers and an anomeric carbon at C-19. Strategically, the exo methylene at C-25 will be incorporated later in the synthesis and will reside in the form of a protected hydroxyl group. The E ring will be constructed by formation of the O/C-26 bond from a hydroxy olefin precursor *via* an electrophilic cyclization. The construction of the carbon skeleton corresponding to the E ring will depend on two stereoselective carbon-carbon bond forming reactions. Firstly, installation of a three carbon synthon represented by an organostannane **9** will incorporate the C-25 through C-27 portion of the E ring. The key transformation is an enantio- and diastereoselective aldol condensation creating the required *anti* stereochemical relationship between C-22/C-23. This bond construction will utilize an optically pure C2 symmetric vinylogous urethane lactone (VUL) enolate as the source of chirality. The protecting groups were chosen in order to facilitate the selective deprotection at an appropriate point later in the synthesis. In addition the protecting group at C-23 was selected to support a chelation controlled addition of a nucleophile, thus large protecting groups such as TBS were avoided.

Recent studies from the Schlessinger group have detailed the application of VUL enolates in *anti* selective aldol condensation reactions which provide the desired adducts with exclusive reaction occurring at the γ -position of the enolate.⁴ To this end, deprotonation of the vinylogous urethane lactone **2** by treatment with

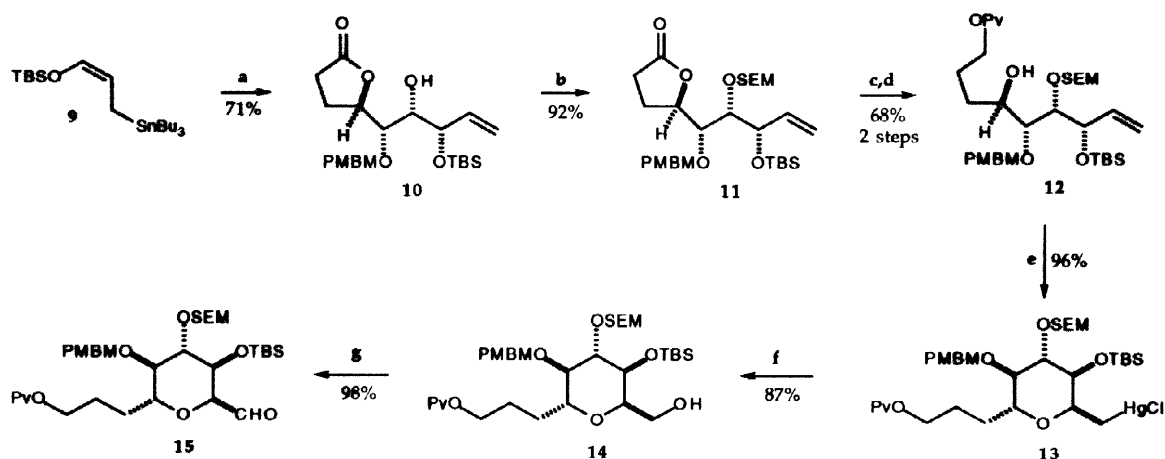
t-BuLi and condensation of the resulting enolate in the presence of DMPU with 3-methyl-2-butenal produced the *anti* lactone **4** and the *syn* lactone **3** in an 8.4:1 ratio.⁵ The stereoselectivity of this aldol process can be rationalized by the *syn*clinal approach of the *Re* face of the aldehyde to the more accessible *Si* face of the VUL enolate through a dipole stabilized transition state.⁶

The crude reaction mixture consisting of *syn* and *anti* aldol adducts **3** and **4** respectively as well as DMPU was treated with diisopropylethylamine and *p*-methoxybenzyloxymethyl chloride (PMBMCl)⁷ in CH₂Cl₂ to afford the ether **5**. Only the *anti* aldol adduct reacted with the PMBMCl, which facilitated the separation of the two diastereomers. At this juncture in the synthetic strategy the vinylogous urethane lactone ring was converted to the saturated analog by a three step procedure. Reduction of the C-20/C-21 olefin occurred by treatment with sodium cyanoborohydride in acetic acid.⁸ Heating the crude reaction mixture to 40°C resulted in a facile β -elimination of the chiral auxiliary to furnish the unsaturated butenolide **6**. The (*R,R*)-*trans*-2,5-dimethylpyrrolidine auxiliary could be recovered in 80% yield. The unsaturated lactone **6** could be reduced by *in situ* generated cobalt boride to afford the saturated lactone **7**.⁹ Ozonolysis of **7** then provided aldehyde **8** in high yield (Scheme 2).¹⁰



Scheme 2: (a) (1) *t*-BuLi, DMPU, THF, -78°C (2) 3-methyl-2-butenal (b) PMBMCl, *i*-Pr₂NEt, CH₂Cl₂ (c) NaCNBH₃, CH₃CO₂H, 23° to 40°C (d) NaBH₄, CoCl₂·6H₂O, CH₂Cl₂, CH₃OH, 23°C (e) (1) O₃, -78°C, CH₃OH, CH₂Cl₂ (2) DMS, 23°C

The union of a three carbon unit and the aldehyde **8** will provide the entire carbon framework of the tetrahydropyran segment of **1**. Thus, condensation of the aldehyde **8** and the γ -siloxyallylstannane **9**, under the conditions described by Keck,¹¹ provided the homoallylic alcohol **10** as the major diastereomer.¹² The formation of the *syn, syn* adduct **10** can be rationalized by an α -chelation model.¹³ Approach of the allylstannane occurs on the less hindered face of the 5-membered magnesium chelate *anti* to the bulky lactone moiety. The reaction proceeds through an antiperiplanar transition state which involves a *Re-Re* combination of the allylstannane and the aldehyde. This acyclic transition state has been proposed by Yamamoto to rationalize the stereoselectivity of the Lewis acid catalyzed addition of crotylstannane to aldehydes.¹⁴



Scheme 3: (a) **8**, $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -20° to 23°C (b) SEMCl, $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2 , 23°C (c) LiHBEt_3 , THF, 23°C (d) PvCl , pyridine, DMAP, 23°C (e) (1) $\text{Hg}(\text{OAc})_2$, THF, 23°C (2) KCl, H_2O (f) NaBH_4 , DMF, O_2 , 23°C (g) $(\text{COCl})_2$, DMSO, TEA, CH_2Cl_2 , -78° to 0°C

The C-24 hydroxyl group was protected as the SEM ether **11**.¹⁵ In order to form the desired tetrahydropyran it is necessary to free the hydroxyl group at C-22 in lactone **11**. Thus, reduction of the lactone carbonyl was effected by treatment of **10** with Super Hydride[®] at ambient temperature to furnish the diol.¹⁶ Selective protection of the primary alcohol as the pivalate in compound **12** set the stage for the critical hydroxymercuration reaction. This cyclization reaction followed the precedent already established by Sinäy and coworkers.¹⁷ Hydroxymercuration of the olefin **12** in the presence of $\text{Hg}(\text{OAc})_2$ followed by ligand exchange gave the organomercury compound **13** as a single diastereomer. The stereoselectivity of the process can be explained by invoking the Houk's inside alkoxy model for the approach of the mercurinium ion and the C-26/C-27 olefin.¹⁸ Cyclization of this Hg^{2+} activated alkene will then proceed through a chair transition state to afford the observed product **13**. The conversion to the desired alcohol **14** was accomplished by the slow addition of an oxygenated solution of NaBH_4 to a solution of **13** in the presence of a rapid stream of oxygen.¹⁹ The synthesis of segment **15** was completed by oxidation of the primary alcohol **14** to the corresponding aldehyde under Swern conditions.

In conclusion, the C-19 through C-27 segment of okadaic acid has been synthesized in 12 steps with an overall yield of 26%. The preparation of this portion of okadaic acid exemplifies the utility of VUL enolates as four carbon synthons in their enantioselective aldol reactions. The remaining stereocenters were introduced using two diastereoselective reactions, namely condensation of a γ -oxygenated allylstannane with the aldehyde **8** and a hydroxymercuration to assemble the tetrahydropyran ring of **1**.

Acknowledgments. Financial support from the NIH, Sherman Clarke, Merck Sharp and Dohme and a Lattimore fellowship are gratefully acknowledged.

References and Notes

Dedicated to the memory of Professor Richard H. Schlessinger
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