ORGANIC LETTERS

1999
Vol. 1, No. 3
451−453

Abbreviated Synthesis of the C3–C14 (Substituted 1,7-Dioxaspiro[5.5]undec-3-ene) System of Okadaic Acid

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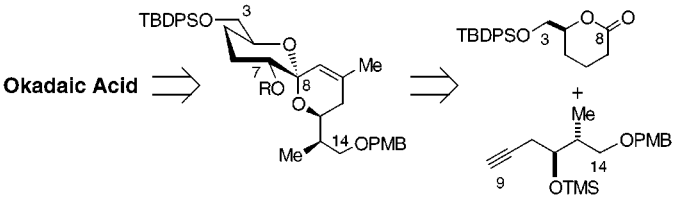
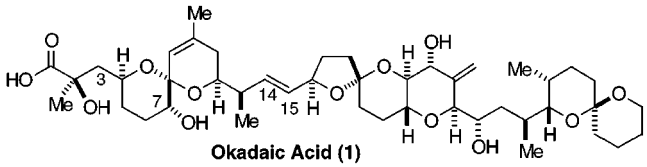
Received May 12, 1999

ABSTRACT



Described is a novel, concise, and flexible synthesis of the C3–C14 portion of okadaic acid. A substituted valerolactone (C3–C8) was prepared in three steps and α-hydroxylated using Davis' oxaziridine. Conjugate addition of dimethylcuprate upon ynones derived from the C3–C8 lactones followed by intramolecular ketalization provided the C3–C14 fragment and revealed a significant role of the C7 α′-ketone substituent upon the efficiency of spiroketalization.

Okadaic acid (**1**) is a notorious marine natural product that has been the focus of a resurgence of synthetic interest.[1−7] We recently described a total synthesis of **1** that relied upon the convergent coupling of three separate polyether-bearing fragments.[2,3]



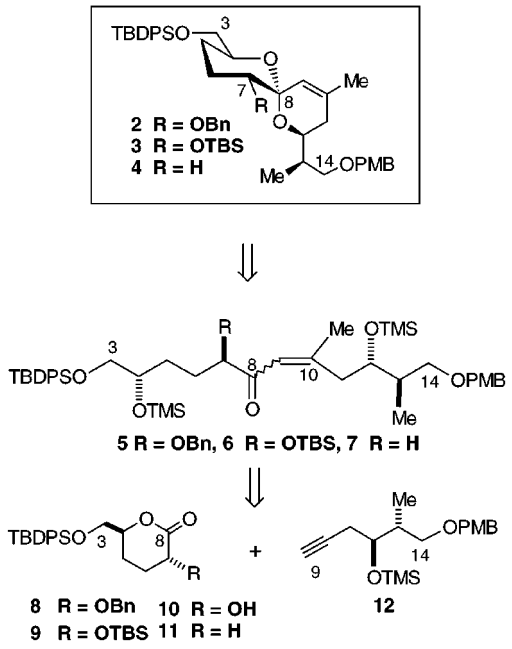
Okadaic Acid (1)

The C1−C14 fragment was elaborated from spiroketal **2**, which in turn was prepared by intramolecular ketalization of enone **5** (Scheme 1).[3] In an approach similar to that used in the original synthesis of **1**,[1] enone **5** was obtained from lactone **8** and alkyne **12**.[3] This involved acetylide anion addition to the lactone, followed by installation of the C10 methyl group by 1,4-addition of dimethylcuprate[8] to the derived ynone. Subsequent treatment of the resultant latent δ,δ′-dihydroxy enone under acidic conditions provided the (8*R*)-spiroketal (**2**), but in only modest yields.[3,9] Furthermore, synthetic access to lactone **8** proved cumbersome,[10] reductive debenzylation in the final step of the published total syntheses of **1** has been problematic,[1,3,4] and C7 variants would be

(1) Isobe, M.; Ichikawa, Y.; Goto, T. *Tetrahedron Lett.* **1986**, *27*, 963.
(2) Urbanek, R. A.; Sabes, S. F.; Forsyth, C. J. *J. Am. Chem. Soc.* **1998**, *120*, 2523.
(3) Sabes, S. F.; Urbanek, R. A.; Forsyth, C. J. *J. Am. Chem. Soc.* **1998**, *120*, 2534.
(4) Ley, S. V.; Humphries, A. C.; Eick, H.; Downham, R.; Ross, A. R.; Boyce, R. J.; Pavey, J. B. J.; Pietruszka J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3907.
(5) Marko, I. E.; Dobbs, A. P.; Scheirmann, V.; Chelle, F.; Bayston, D. J. *Tetrahedron Lett.* **1997**, *38*, 2899.
(6) Marko, I. E.; Chelle, F. *Tetrahedron Lett.* **1997**, *38*, 2895.
(7) Dankwardt, S. M.; Dankwardt, J.; Schlessinger, R. H. *Tetrahedron Lett.* **1998**, *39*, 4983 and preceding papers in that issue.
(8) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851.
(9) Ichikawa, Y.; Isobe, M.; Bai, D.-L.; Goto, T. *Tetrahedron* **1987**, *43*, 4737.
(10) Lactone **8** was prepared previously in eight steps from D-2-acetoxytriacetylglucal.[3]

10.1021/ol9906615 CCC: $18.00
Published on Web 06/22/1999

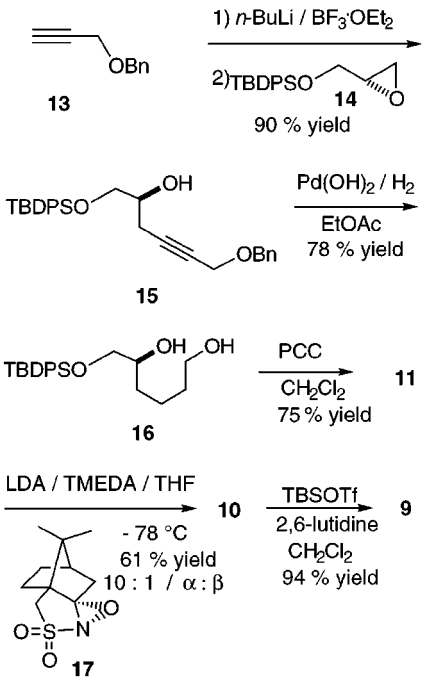
Scheme 1. Retrosynthesis of the C3−C14 Domain



useful for biological studies. Hence, a new concise and flexible synthesis of the C3−C8 lactone was developed and used to prepare C7-functionalized derivatives of the (8*R*)-1,7-dioxaspiro[5.5]undec-3-ene system of **1**.

Lactone **11**[11] was prepared in three steps from benzyl propargyl ether (**13**) and silylated glycidol **14** (Scheme 2). Opening of epoxide **14** with the acetylide anion derived from **13** under Yamaguchi conditions[12] gave **15**. Hydrogenation

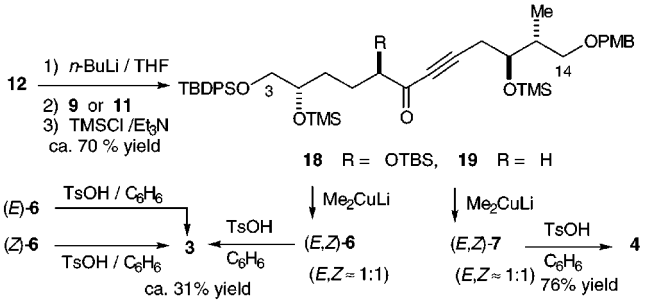
Scheme 2. Synthesis of C3−C8 Lactone



then provided diol **16**. Oxidation of **16** with PCC (CH_2Cl_2, 4 Å MS, rt) conveniently delivered lactone **11**, as well as minor amounts of the corresponding keto-aldehyde. Diastereoselective α-hydroxylation of **11** was effected with Davis' chiral oxaziridine **17**.[13] Treatment of the lithium enolate of lactone **11** with **17** in the presence of TMEDA followed by careful quench with CSA gave α-hydroxy lactone **10** in moderate yield. The hydroxyl group could be benzylated under nonbasic conditions[14] to yield the known okadaic acid intermediate **8** via this dramatically abbreviated route.[10] However, the C7 hydroxyl group was alternatively masked as a TBS ether (**9**) at this stage to facilitate final deprotection.

To determine the utility of the C7 variants for formation of spiroketals **3** and **4**, ynones **18** and **19** were prepared from alkyne **12**[3] and the corresponding lactones **9** and **11** (Scheme 3).[15] Conjugate addition of dimethylcuprate to **18** or **19**

Scheme 3. Synthesis of C3−C14 Spiroketals



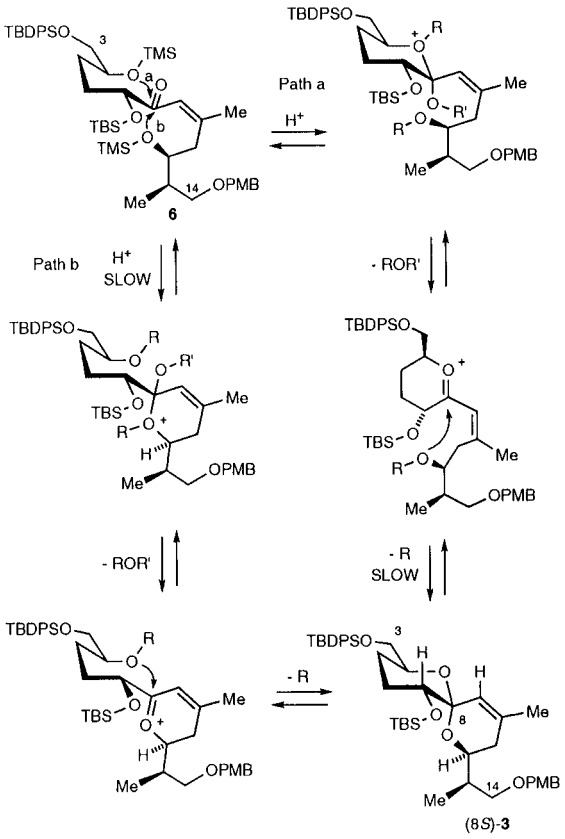
provided nearly quantitative yields of enones **6** or **7**, respectively, each as an approximate 1:1 mixture of (*E*,*Z*)-isomers.[16] TsOH-induced spiroketalization of the (*E*,*Z*)-mixture of **6** generated (8*R*)-spiroketal **3** in 31% yield, comparable to the yield obtained for the conversion of **5** to **2** in the total synthesis of **1**.[3] Similar yields of **3** were obtained from chromatographically separated samples of (*E*)-**6** and (*Z*)-**6** upon subjection of each to the ketalization conditions. However, treatment of the (*E*,*Z*)-mixture of **7** under the same conditions remarkably generated (8*R*)-spiroketal **4** in higher yield (76%). Because the starting enone configuration has little impact on the overall efficiency of the bicyclodehydration, the limited yield of spiroketal **3** obtained via the conjugate addition−spiroketalization sequence may largely be attributable to the presence of the substituent at C7. Spiroketalization may be initiated by a relatively unencumbered attack of the C4 oxygen upon the central C8 ketone (path a, Scheme 4), followed by capture of an oxocarbenium intermediate by an impeded C12 oxygen.

(11) All new compounds gave characterization data that are fully consistent with the structures assigned.

(12) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.
(13) Davis, F. A.; Kumar, A. *J. Org. Chem.* **1992**, *57*, 3337.
(14) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.
(15) Chabala, J. C.; Vincent, J. E. *Tetrahedron Lett.* **1978**, 937.

(16) The ratios of (*E*,*Z*)-isomers of **6** and **7** were assigned by integration of the vinylic proton and methyl resonances in the ^{1}H NMR spectra of the crude conjugate addition products.

Scheme 4. C7 Substituent Effect on Spiroketalization



Alternatively, a sterically disfavored initial addition of the C12 oxygen to C8 (path b) would be followed by closure of the spirocycle by the C4 oxygen. In either path, attack of the C12 oxygen upon an sp^2-hybridized carbon at C8 is expected to be sterically hindered by the substituent at C7.[17]

This study defines improved synthetic access to two key okadaic acid intermediates, differentially protected lactone **9** and spiroketal **3**. Although the yield of the spiroketalization step to form the bis-silyl ether **3** is comparable to that for the formation of **2**,[3] the use of a fluoride-labile protecting group for the C7 hydroxyl obviates the necessity for an ultimate reductive deprotection.[18] Combined, these findings will contribute to further syntheses of okadaic acid. Moreover, omission of C7 functionalization altogether facilitates dramatically the key spiroketalization process, which will support the generation of analogues of okadaic acid lacking the C7 hydroxyl group.

Acknowledgment. Financial support of this research from an American Chemical Society Division of Medicinal Chemistry Graduate Fellowship sponsored by Parke-Davis and a University of Minnesota Graduate School Fellowship (A.B.D.) as well as a University of Minnesota McKnight Land-Grant Professorship, a Zeneca Pharmaceuticals Excellence in Chemistry Award, and the NIH (CA62195) (C.J.F.) is gratefully acknowledged. We also thank Drs. S.F. Sabes (Shionogi BioResearch Corp.) and R.A. Urbanek (AstraZeneca) for helpful discussions.

OL9906615

(17) This problem is nicely avoided in the recently reported synthesis of **1** by Ley et al.[4]

(18) The primary TBDPS ether of **3** could be cleaved selectively in the presence of the secondary TBS ether using TBAF to generate the synthetically viable[3] primary alcohol in 61% yield.