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Multicomponent Condensations—Model Studies Towards an Efficient Synthesis of Okadaic Acid

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Abstract: The model spiroketal **19** and dioxadecalin **36** have been readily assembled with full stereocontrol using novel multicomponent condensation strategies.

Okadaic acid **1** is a complex natural product isolated by Tachibana et al. from the marine sponges *Halichondria okadai* and *Halichondria melanodocia* (Figure 1).[1] Together with its congeneers, acanthifolicin[2] and the dinophysistoxins,[3] okadaic acid is present during the marine red tides. It is a potent member of the Diarrhetic Shellfish family toxins and causes one of the most prevalent types of poisoning occuring in Europe. Okadaic acid also exhibits powerful biological activities. It is not only a selective protein phosphatase inhibitor but it also interacts with cellular regulatory processes and is a potent tumour promoter.[4]

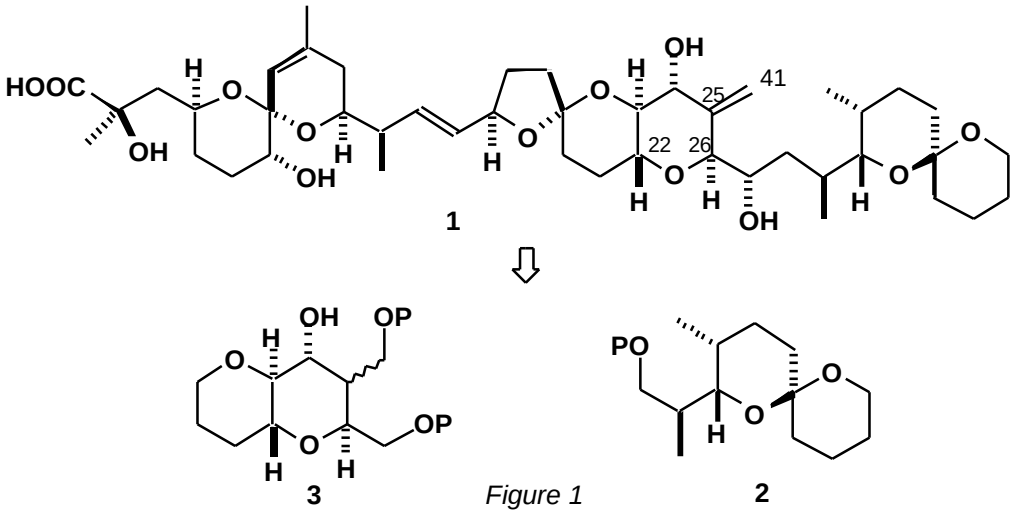


Figure 1

*Invited lecture presented at the International Conference on Biodiversity and Bioresources: Conservation and Utilization, 23–27 November 1997, Phuket, Thailand. Other presentations are published in *Pure Appl. Chem.*, Vol. 70, No. 11, 1998.

As part of a major research programme directed towards understanding, at the molecular level, the selective inhibition of protein phosphatases and its impact on cellular regulation and carcinogenesis, we became interested in the total synthesis of okadaic acid. This marine toxin is a formidable target, embodying, in its complex architectural framework, no less than seventeen chiral centres, several spiroketal subunits and a dioxadecalin fragment. To-date, only two total synthesis of okadaic acid **1** have been reported: the first one by Isobe *et al.*,[5] and the second by Forsyth *et al.*.[6] Unfortunately, neither of them are amenable to analogue preparation and to the study of structure-activity relationships. In this article, we wish to report some of our results directed towards the development of a concise and flexible approach to both the eastern spiroketal subunit **2** and the central dioxadecalin fragment **3** based on a multicomponent condensation strategy.

We envisioned that the eastern spiroketal portion of **1** could be constructed by the short sequence of steps illustrated in Figure 2.

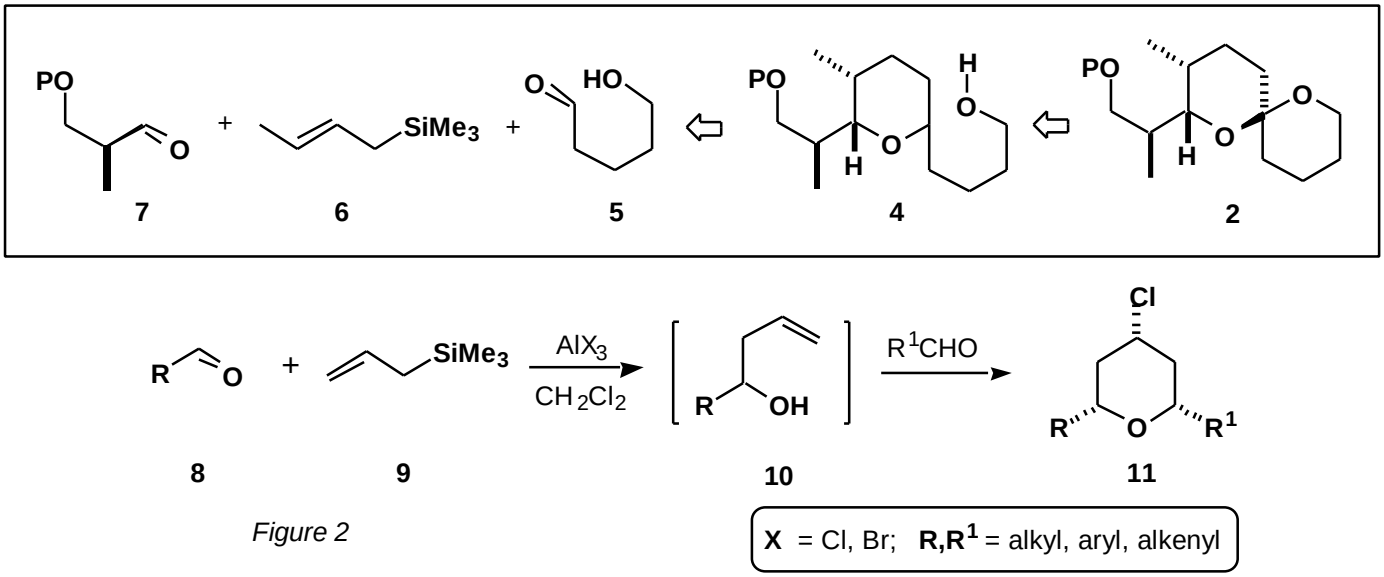
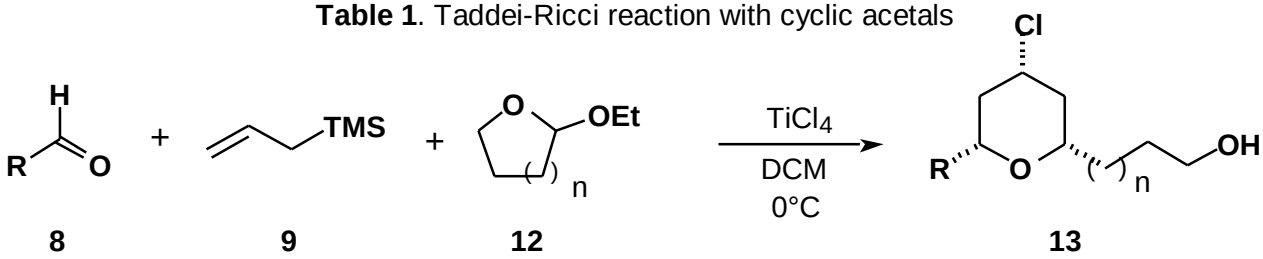


Figure 2

Antithetic analysis of fragment **2** reveals the hydroxy tetrahydropyran **4** as a key-intermediate. We envisaged that **4** could be accessed in a single step from the simple starting materials **5**, **6** and **7** *via* a modification of the Taddei-Ricci protocol.[7]

This exquisite, though little used methodology involves the Lewis-acid mediated condensation of allyltrimethylsilane with two equivalents of an aldehyde (Figure 2). In the presence of strong Lewis acids such as $AlBr_3$ or $AlCl_3$, halide-containing tetrahydropyrans **11** are obtained in good yields. In order to incorporate the ω-hydroxyl function present in our key-intermediate **4**, we investigated the non-symmetrical Taddei-Ricci coupling between selected aldehydes and cyclic acetals (Table 1).

Table 1. Taddei-Ricci reaction with cyclic acetals



8 **9** **12** **13**

Entry	RCHO	n	Product	Yield
1	$C_6H_{13}CHO$	1	**13a**	62 %
2	$(C_2H_5)_2CHCHO$	1	**13b**	77 %
3	$C_6H_{13}CHO$	2	**13c**	60 %
4	$(C_2H_5)_2CHCHO$	2	**13d**	60 %

Gratifyingly, both 2-ethoxy-tetrahydropyran and 2-ethoxy-tetrahydrofuran underwent smooth condensation with allyltrimethylsilane and a variety of aldehydes, to afford in good yields the desired heterocycles **13** (Table 1). In this process, $TiCl_4$ proved to be superior to other Lewis acids such as $AlCl_3$ and $AlBr_3$. It is noteworthy that this four-component condensation reaction generates a single diastereoisomer of the pyran-derivatives **13** with complete control of the relative stereochemistry of all the chiral centres. Reductive dechlorination using $NaBH_4$ in HMPA proceeded quantitatively.[8] Oxidative cyclisation using HgO and I_2 eventually afforded the final spiroketals **15** in excellent overall yields (Figure 3).[9]

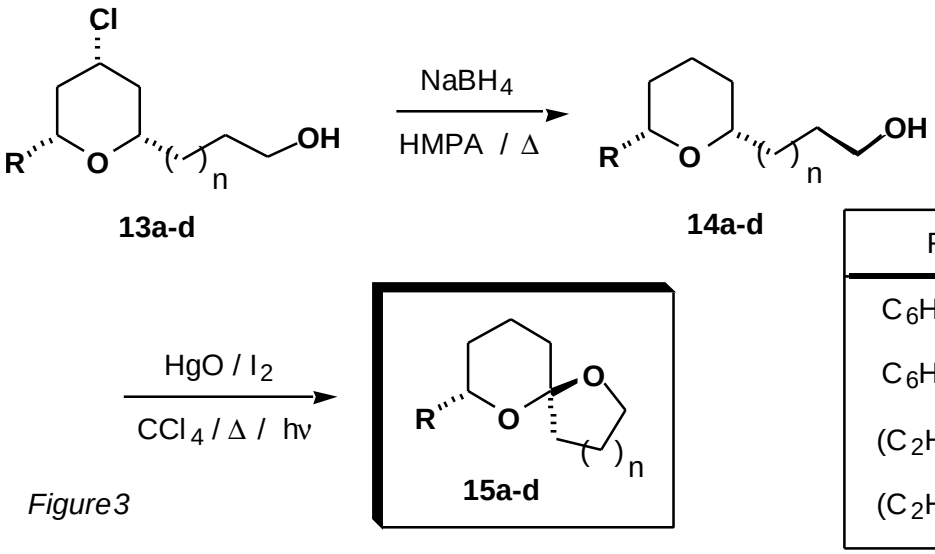


Figure 3

R	n	Product	Yield
C_6H_{13}	1	**15a**	67 %
C_6H_{13}	2	**15c**	77 %
$(C_2H_5)_2CH$	1	**15b**	64 %
$(C_2H_5)_2CH$	2	**15d**	72 %

Having established the viability of this novel methodology, we then turned our attention to the incorporation of the C_3 methyl substituent. Application of this approach would require the use of crotyltrimethylsilane **6** instead of allyltrimethylsilane **9**. Unfortunately, early attempts to condense crotyltrimethylsilane repeatedly failed. Success was eventually achieved by using carefully purified **6** and rigorous control of the reaction conditions (Figure 4).

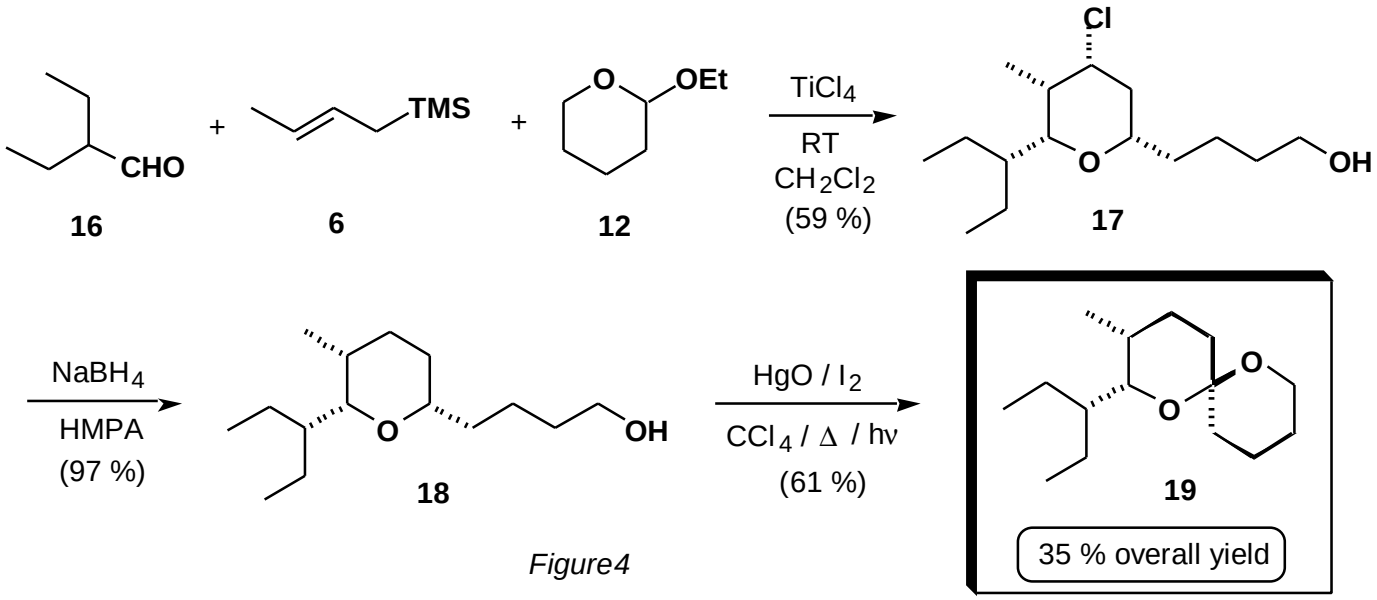


Figure4

The relative stereochemistry of all the chiral centres of **17** was unambiguously established through careful spectroscopic analysis. These studies revealed that the substituents of the pyran nucleus are all *cis* to each other and that the methyl group occupies an axial position; the remaining three substituents all being equatorially disposed. The observed stereochemical control results directly from the open-transition state typically encountered in these reactions. Finally, reduction and oxidative cyclisation concluded this model study, affording compound **19** in an overall yield of 35% ! Having demonstrated that an efficient and flexible route to a variety of polysubstituted spiroketals related to the eastern portion of okadaic acid was now available, we turned our attention to some model studies towards the middle fragment **3**.

Retrosynthetic analysis of subunit **3** suggested the trisubstituted dihydropyran **20** as a key-intermediate (Figure 5). We envisioned preparation of **20** by using the Intramolecular Silyl-Modified Sakurai (ISMS) reaction between vinylsilane **21** and ethoxy-tetrahydrofuran **12**.[10] Such an approach requires an extension of our ISMS procedure to include vinylsilanes as the annelating agents.[11] The successful implementation of this strategy would expand the versatility of our ISMS methodology and open a flexible avenue to a variety of structural motifs present in important natural products.

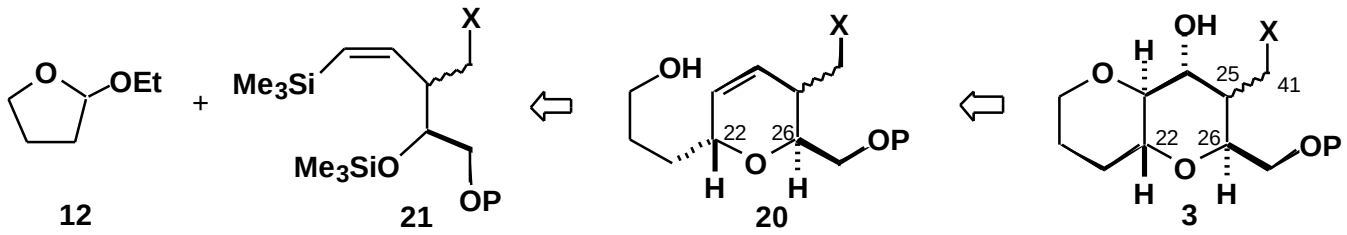


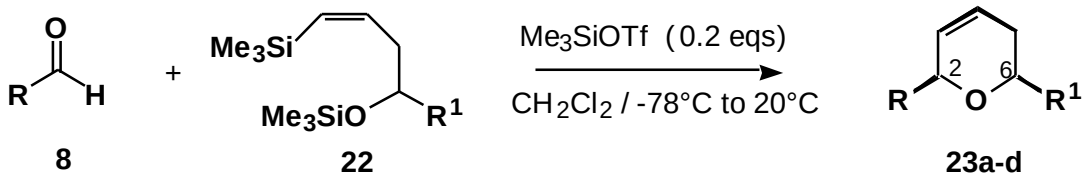
Figure5

X = OR, SR, SeR ; **P** = protecting group

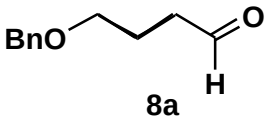
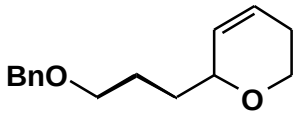
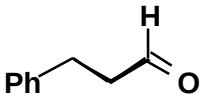
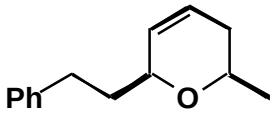
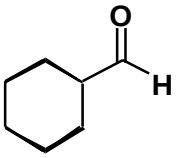
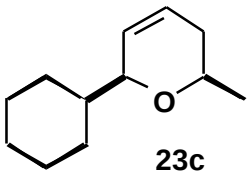
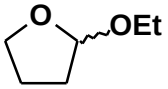
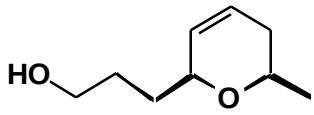
Initial experiments were carried out using the simple vinylsilane **22**. Addition of a catalytic amount of TMSOTf to carbonyl derivatives **8** and vinylsilane **22** smoothly afforded the desired dihydropyrans **23** in good yields (Table 2). In all cases, the 5,6-dihydropyran was obtained with no trace of double bond isomerisation. Moreover, only the 2,6-*syn*-disubstituted diastereoisomer was produced. Unfortunately, this relative stereochemistry is incorrect for the preparation of derivative **20** which possesses a 2,6-*anti*-relationship.

Closer inspection of our antithetic analysis revealed that the stereochemistry of the chiral centre at C_{25} was inconsequential since it was to be obliterated at a later stage to generate the *exo*-methylene double bond (Figure 5). This observation implies that either the *syn*- or the *anti*-annelating agent **21** could be used in the ISMS condensation. We were therefore intrigued by the possibility of exploiting the relative stereochemistry of the annelating agent to control the C_{22}-C_{26} stereochemical relationship of the final pyran derivative. That such a control could indeed be realised was suggested by a detailed examination of the possible transition states of the ISMS reaction between an aldehyde and either *syn*- or *anti*-**21** (Figure 6).

Table 2. Selected Intramolecular Silyl-Modified Sakurai (ISMS) Cyclisations of Vinylsilanes



8 **22** **23a-d**

Entry	RCHO	R^1	Product	Yield
1	 **8a**	H	 **23a**	78 %
2	 **8b**	CH_3	 **23b**	89 %
3	 **8c**	CH_3	 **23c**	87 %
4	 **12**	CH_3	 **23d**	69 %

Intramolecular cyclisation of *syn*-**21** could proceed either *via* transition state **24**, in which three substituents occupy axial positions and which suffers from severe 1,3-diaxal interactions between the $SiMe_3$ group and the C_{25} substituent or *via* transition state **25** containing none of these destabilising interactions. Cyclisation of *syn*-**21** with ethoxy THF should thus afford dihydropyran **29** possessing the undesired *cis*-22,26-relative stereochemistry. Similarly, *anti*-annelating agent **21** could react *via* the two possible transition-states **26** and **27**.

Steric compression between the $SiMe_3$ substituent and the C_{25} moiety should strongly disfavour **27** as compared to **26** in which such diaxal interactions are absent. ISMS cyclisation using *anti*-**21** should thus deliver dihydropyran **30** possessing the correct *trans* relative stereochemistry between C_{22} and C_{26} of subunit **3**.

In the event, ISMS condensation between *anti*-silyl ether **34** and ethoxy THF afforded a single diastereoisomer **35** in excellent yield. The *anti*-relationship between the C_{22} and C_{26} substituents was unambiguously established by X-ray diffraction analysis of a peracylated

derivative of **35**. The formation of *anti*-**35** supports our previous analysis and suggests the chair-like transition state **26** as the preferred one.

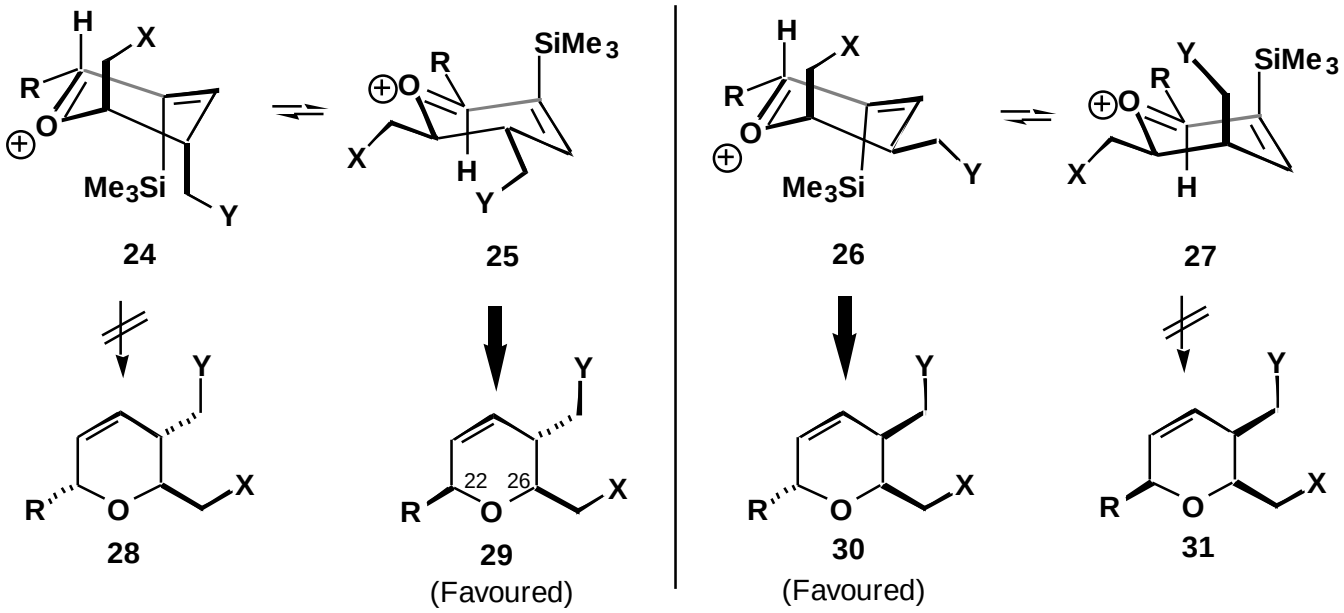


Figure6

The completion of the synthesis of model *trans*-dioxadecalin **36** was expendiently realised by stereoselective expoxidation from the α-face followed by cyclisation under acidic conditions.[12]

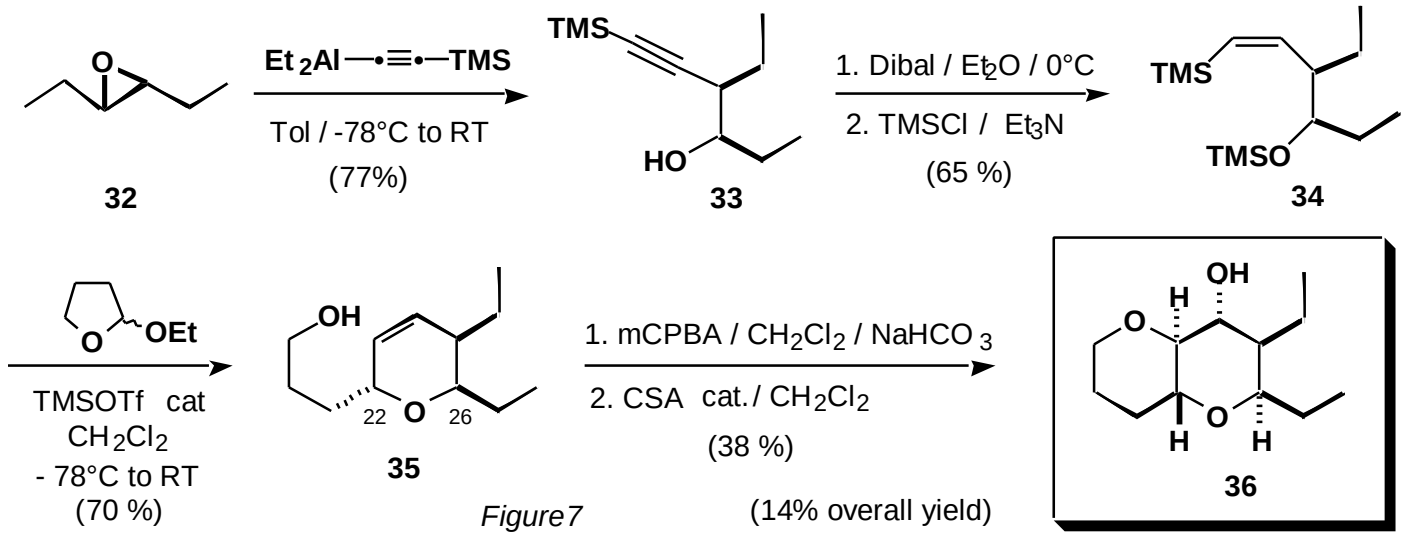


Figure7

In summary, we have developed two simple, efficient and flexible routes towards models of the eastern and middle portions of okadaic acid. The synthesis of OA using these novel approaches is being currently pursued in our laboratory. The results of our investigations will be reported in due course.

ACKNOWLEDGEMENTS

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