Pergamon

Tetrahedron Letters, Vol. 38, No. 16, pp. 2895-2898, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00470-X

Efficient Methodology for the Construction of Substituted Spiroketals. Model Studies towards the Synthesis of the Eastern Spiroketal Subunit of Okadaic Acid.

István E Markó* and François Chellé

Université catholique de Louvain, Département de Chimie, Laboratoire de Chimie Organique, Bâtiment Lavoisier, Place Louis Pasteur 1, 1348 Louvain-la-Neuve, Belgium.

Abstract: the model spiroketal subunit **19**, featuring the eastern fragment of okadaic acid has been assembled in three steps with full regio- and stereo-control.
© 1997 Elsevier Science Ltd.

Okadaic acid **1** is a complex natural product first isolated by Tachibana *et al.* from the marine sponges *Halichondria okadai* and *Halichondria melanodocia* (Figure 1).[1] Together with its congeners, acanthifolicin[2] and the dinophysistoxins,[3] okadaic acid is present during the marine red tides generated by the explosive proliferation of certain dinoflagellates.[4] Okadaic acid is a member of the Diarrhetic Shellfish Poisoning family of marine toxins which cause the most prevalent type of poisoning occuring in Europe. Besides its challenging architectural framework, which embodies seventeen chiral centres and three spiroketal subunits, okadaic acid exhibits powerful biological activities, such as highly selective protein phosphatase inhibition.[5] It is also a tumour promoter[6] and interacts with cellular regulatory processes.[7]

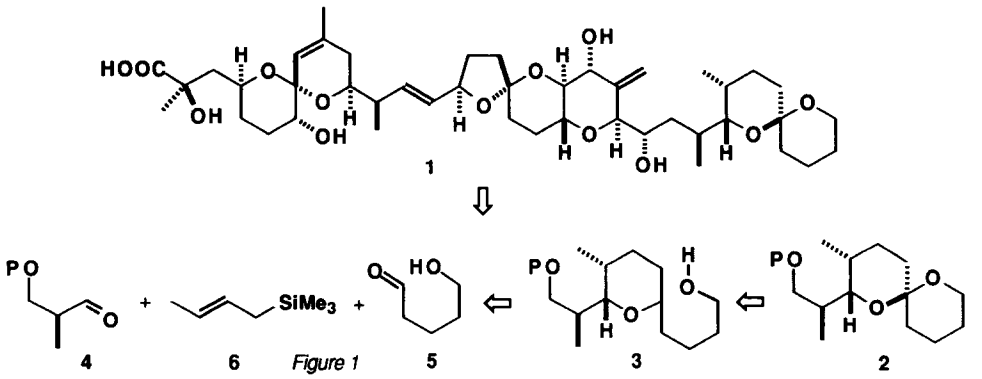


Figure 1

As part of a major research program aimed at understanding, at the molecular level, the biological effect of selective protein phosphatase inhibitors on cellular regulation and carcinogenesis, we became interested in the preparation of okadaic acid. To date, only one total synthesis of okadaic acid has been reported by Isobe *et al.*[8] Unfortunately, this landmark synthesis is not ameanable to analogue preparation and to the study of structure-activity relationship.

In this letter, we wish to report a concise synthesis of a model spiroketal, which mimics the eastern fragment of okadaic acid, and the establishment of flexible methodology for the assembly of such spiroketals, which features a three component-coupling reaction as the key-step.

Antithetic analysis of the eastern subunit **2** of okadaic acid reveals the hydroxy-tetrahydropyran **3** as a key intermediate. We envisioned generation of **3** in a single step *via* a modified version of the Taddei-Ricci condensation[9] (Figure 2). This exquisite, though little used, methodology involves the condensation of allyltrimethylsilane with two equivalents of an aldehyde, in the presence of strong Lewis acids, such as $AlCl_3$ or $AlBr_3$, to produce halide-containing tetrahydropyran derivatives **10** in good yields.

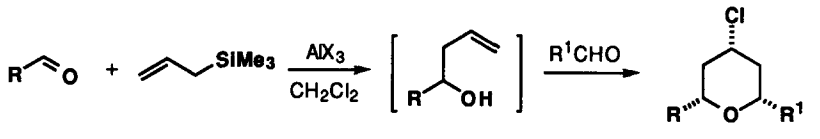
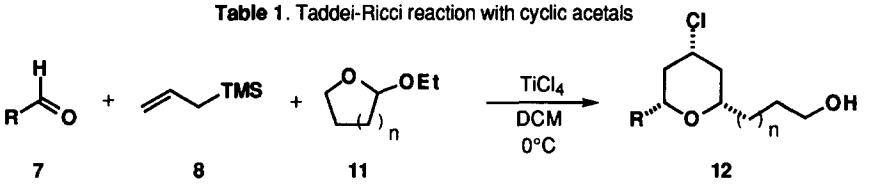


Figure 2

X = Cl, Br; **R,R^1** = alkyl, aryl, alkenyl

In order to incorporate the hydroxyalkane side-chain required for the oxidative-cyclisation of **3** into spiroketal **2**, we investigated the Taddei-Ricci condensation of selected aldehydes with cyclic acetals. Pleasingly, addition of 2-ethoxy-tetrahydrofuran or 2-ethoxy-tetrahydropyran to an aldehyde, allyltrimethylsilane and titanium tetrachloride, resulted in the smooth formation of the desired six-membered heterocycles **12** in good yield (Table 1). The generation of hydroxyl-containing THP derivatives **12** demonstrates that cyclic acetals can be effectively used in this condensation as cheap and easy-to-handle substitutes for protected ω-hydroxy alkanals.[10] It is noteworthy that a single diastereoisomer is produced in this reaction; the three substituents occupying equatorial positions.[11] We also observed that $TiCl_4$ was a much better promoter than aluminium salts in the acetal cyclisations, affording better yields and cleaner reaction mixtures.

Table 1. Taddei-Ricci reaction with cyclic acetals



Entry	RCHO	n	Product	Yield
1	$C_6H_{13}CHO$	1	**12a**	62 %
2	$(C_2H_5)_2CHCHO$	1	**12b**	77 %
3	$C_6H_{13}CHO$	2	**12c**	60 %
4	$(C_2H_5)_2CHCHO$	2	**12d**	60 %

Reductive dechlorination of **12**, using the excellent Hutchins protocol[12], ($NaBH_4$ in hot HMPA) gave tetrahydropyrans **13** quantitatively (Figure 3). Oxidative-cyclisation, mediated by HgO/I_2 generated the desired spiroketals **14** in good overall yields.[13]

Having established a rapid access to various functionalised spiroketals **14**, we next turned our attention to methods for the introduction of the C_{31} methyl substituent of okadaic acid. Application of our route to the preparation of model compound **19** would require the use of crotyltrimethylsilane as one of the components in

the Taddei-Ricci reaction. Unfortunately, early attempts to condense substituted allylsilanes failed to produce any cyclisation product.[14] After several unsuccessful trials, we found that the use of $TiCl_4$ and rigorously purified crotyltrimethylsilane smoothly afforded the desired tetrasubstituted tetrahydropyran **17** (Figure 4).

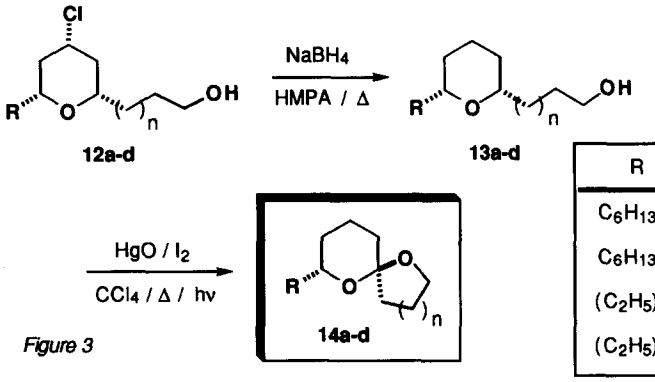


Figure 3

R	n	Product	Yield
C_6H_{13}	1	**14a**	67 %
C_6H_{13}	2	**14c**	77 %
$(C_2H_5)_2CH$	1	**14b**	64 %
$(C_2H_5)_2CH$	2	**14d**	72 %

The relative stereochemistry of the four substituents of **17** was unambiguously established through careful spectroscopic analysis and found to be all-*cis*, i.e. the methyl group occupies an axial position while the other substituents are all located equatorially.[15] This diastereoselectivity results directly from the open transition state which typically occurs in the addition of allylsilanes to carbonyl derivatives.[16] Reductive dechlorination of **17** with $NaBH_4$ followed by mercuric oxide promoted cyclisation gave the desired model spiroketal **19** in 35% overall yield.

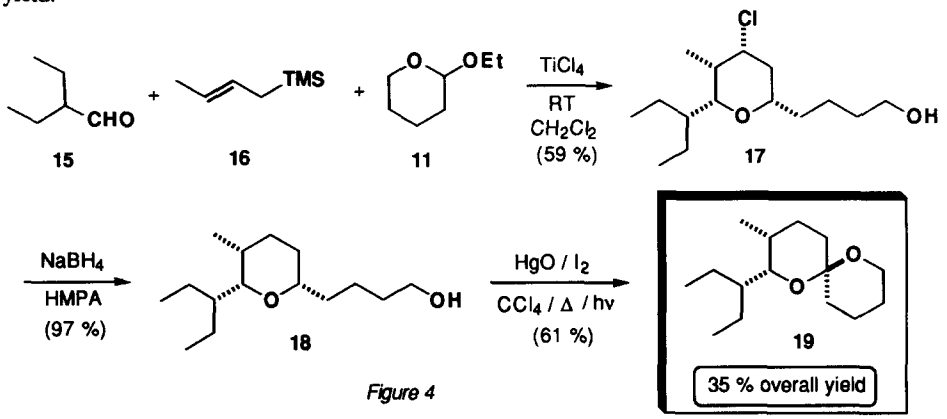


Figure 4

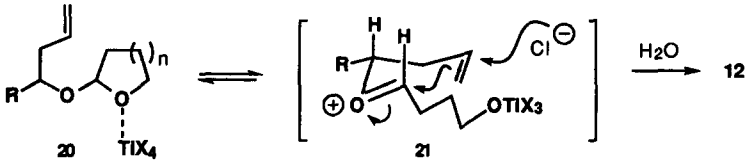
In summary, we have described a particularly short and efficient route for the preparation of a variety of substituted spiroketals. In particular, this methodology has enabled the three step assembly of the model compound **19**, which embodies all the structural motifs of the eastern subunit **2** of okadaic acid. The synthesis of **2**, using these methods is being actively pursued in our laboratory and the results of our investigations will be reported in due course.

Acknowledgements

Financial support by the Région wallonne, contrat FIRST N°2645, the Université catholique de Louvain and Merck (Rahleigh, NJ) is warmly acknowledged. IEM is grateful for a Zeneca Fellowship and for a Sandoz Lectureship.

References and Notes

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.
2. Schmitz, F.J.; Prasad, R.S.; Gopichand, Y.; Hossain, M.B.; van der Helm, D.; Schmidt, P. *J. Am. Chem. Soc.*, **1981**, *103*, 2467.
3. Murata, M.; Shimatani, M.; Sugitani, H.; Oshima, Y.; Yasumoto, T. *Bull. Japan Soc. Sci. Fish.*, **1982**, *48*, 549.
4. Although okadaic acid was isolated from marine sponges, contaminating dinoflagellates are responsible for the production of this toxin. Murakami, Y.; Oshima, Y.; Yasumoto, T. *Bull. Japan Soc. Sci. Fish.*, **1982**, *48*, 69. For an excellent review on Ciguatera and its off-shoots, see: Scheuer, P.J. *Tetrahedron*, **1994**, *50*, 3.
5. Cyert, M.S.; Thorner, J. *Cell*, **1989**, *57*, 891.
6. Nishiwaki, S.; Fujiki, H.; Saganuma, M.; Furuya-Suguri, H.; Matsushima, R.; Iida, Y.; Ojika, M; Yamada, K.; Uemura, D.; Yasumoto, T.; Schmitz, F.J.; Sugimura, T. *Carcinogenesis*, **1990**, *11*, 1837.
7. Cohen, P.; Holmes, C.F.B.; Tsukitani, Y. *Trends Biochem. Sci.*, **1990**, *15*, 98. See also: Brugge, J.S. *Chem. Biol.*, **1994**, introductory issue.
8. Isobe, M.; Ichikawa, Y.; Bai, D.-L.; Masaki, H.; Goto, T. *Tetrahedron*, **1987**, *43*, 4767 and references cited therein.
9. (a) Coppi, L.; Ricci, A.; Taddei, M. *Tetrahedron Lett.*, **1987**, *28*, 973; (b) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.*, **1988**, *53*, 911. See also: (a) Wei, Z.Y.; Li, J.S.; Wang, D.; Chan, T.H. *Tetrahedron Lett.*, **1987**, *28*, 3441; (b) Wei, Z.Y.; Wang, D.; Li, J.S.; Chan, T.H. *J. Org. Chem.*, **1989**, *54*, 5768.
10. The reaction probably proceeds by initial transacetalisation of the homoallylic alcohols **9** with ethoxy THF (THP) affording acetal **20**. Activation of the endocyclic oxygen by $TiCl_4$, followed by opening of the heterocycle generates the oxonium ion **21** which is then intercepted by the incipient allylic residue.



20 21

11. The observed stereochemistry corroborates the observations of Taddei and Ricci and is easily deduced from the analysis of the NMR spectra of compounds **12**. It originates from the chair-like transition state **21**.
12. (a) Hutchins, R.O.; Hoke, D.; Keogh, J.; Koharski, D. *Tetrahedron Lett.*, **1969**, 3495; (b) Hutchins, R.O.; Kandasamy, D.; Dux III, F.; Maryanoff, C.A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.*, **1978**, *43*, 2259.
13. (a) Mihailovic, M.L.; Cekovic, Z.; Stankovic, J. *J. Chem. Soc., Chem. Commun.*, **1969**, 981; (b) Danishefsky, S.J.; Armistead, D.M.; Wincott, F.E.; Selnick, H.G.; Hungate, R. *J. Am. Chem. Soc.*, **1989**, *111*, 2967; (c) Martin, A.; Salazar, J.A.; Suárez, E. *Tetrahedron Lett.*, **1995**, *36*, 4489.
14. This failure was also noticed by Taddei and Ricci (Taddei, M., Personal communication).
15. For example, H^4 appears in the ^1H NMR spectrum of **17** as a dt (J^1 = 12 Hz; J^2 = 4.5 Hz) while it forms a tt (J^1 = 12 Hz; J^2 = 4.4 Hz) in compounds **10**, thus unambiguously positioning the choride and methyl substituents in an equatorial and axial position respectively.
16. (a) Yamamoto Y.; Yatagai, H.; Saito, Y.; Maruyama, K. *J. Org. Chem.*, **1984**, *49*, 1096; (b) Yamamoto Y.; Saito, Y.; Maruyama, K. *J. Organometallic Chem.*, **1985**, *292*, 311.

(*Received in UK* 27 *February* 1997; *accepted* 7 *March* 1997)