Pergamon

Tetrahedron Letters, Vol. 38, No. 16, pp. 2899-2902, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00471-1

Concise and Stereocontrolled Assembly of Substituted Dihydropyrans. Synthetic Studies Towards the *trans*-Dioxadecalin Subunit of Okadaic Acid.

István E Markó*, Adrian P. Dobbs, Vincent Scheirmann, François Chellé and Daniel J. Bayston

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

Abstract: A simple methodology for the stereocontrolled synthesis of dihydropyrans has been established. The *trans*-dioxadecalin **22**, featuring the middle portion of okadaic acid, has been efficiently assembled using this strategy. © 1997 Elsevier Science Ltd.

Okadaic acid **1**, a complex marine toxin responsible for Diarrhetic Shellfish Poisoning possesses intriguing biological activities.[1] Its challenging structural architecture, embodying seventeen chiral centres and several spiroketal subunits, has stimulated our interest in the total synthesis of **1**.[2] In the preceding communication,[3] we have reported a powerful and expedient methodology for the construction of spiroketals which has allowed the rapid assembly of a model for the eastern fragment of okadaic acid.

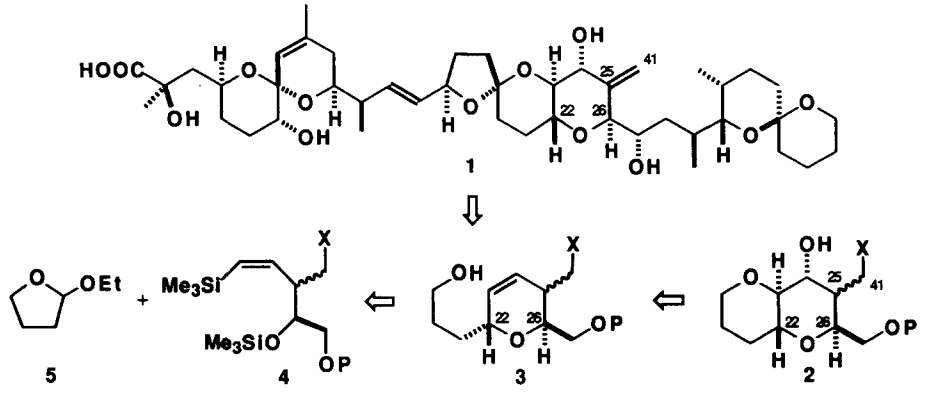


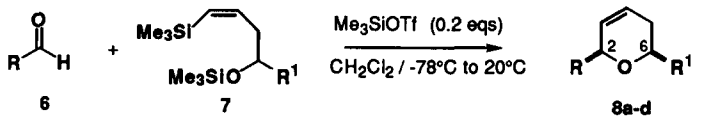
Figure 1

In this letter, we describe a simple approach for the synthesis of polysubstituted dihydropyrans, using as the key-step the Intramolecular Silyl-Modified Sakurai (ISMS) condensation of vinylsilanes.[4] The power of this methodology is illustrated by the preparation of *trans*-dioxadecalin **22**, a model for the middle portion **2** of okadaic acid. Retrosynthetic analysis of fragment **2** (Figure 1) suggested the trisubstituted dihydropyran **3** as a key-intermediate. We envisioned that **3** could be readily obtained by the ISMS reaction of ethoxy tetrahydrofuran **5** with the annelating agent **4**. This strategy requires an extension of our ISMS cyclisation methodology[5] to include vinylsilanes as the nucleophilic component in the ring closing sequence. Such a process is highly attractive as it offers a flexible approach to the regio- and stereo-controlled synthesis of substituted dihydropyrans. Moreover the endocyclic double bond provides versatile functionality for subsequent elaboration to a variety of structural motifs present in important natural products.

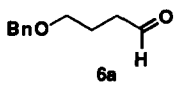
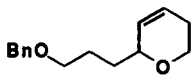
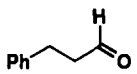
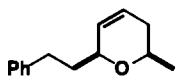
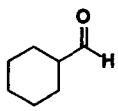
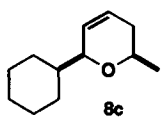
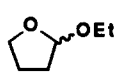
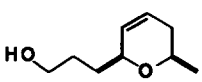
Addition of a catalytic amount of TMSOTf to a solution of aldehyde **6a-c** (or acetal **5**) and vinylsilanes **7**

smoothly afforded the desired dihydropyrans **8a-d** in good yield (Table 1). In all cases, the 5,6-dihydropyran was obtained with no trace of the isomerised 4,5-dihydro-derivative.[6] When the substituted annelating agent **7** (R^1 = Me) was used, the 2,6-*syn*-disubstituted heterocycles **8b-8d** were formed as single diastereoisomers.

Table 1. Selected Intramolecular Silyl-Modified Sakurai (ISMS) Cyclisations of Vinylsilanes



6 + **7** → **8a-d**

Entry	RCHO	R^1	Product	Yield
1	 **6a**	H	 **8a**	78 %
2	 **6b**	CH_3	 **8b**	89 %
3	 **6c**	CH_3	 **8c**	87 %
4	 **5**	CH_3	 **8d**	69 %

These results clearly demonstrated the utility of the ISMS process for the diastereoselective preparation of dihydropyrans. The use of ethoxy-THF **5** allowed the direct incorporation of a useful functionality in dihydropyran **8d**. However, the sense of the 2,6-stereochemical induction in these reactions was opposite to that required for the preparation of **3**, the desired precursor for the synthesis of okadaic acid.

In our retrosynthetic analysis, the C_{25}-C_{41} *exo*-methylene double bond was to be generated by elimination of a sulfoxide or selenoxide from intermediate **2** (Figure 1). The relative stereochemistry between C_{25} and C_{26} in alcohol **2** could thus be either *cis* or *trans*, implying that we could use the *syn*- or *anti*-annelating agents **4** interchangeably. We were intrigued by the possibility of exploiting the relative configuration of the annelating agent to control the stereochemistry between C_{22} and C_{26} during the ISMS cyclisation. Detailed examination of the four possible transition states **9** to **12** revealed interesting differences (Figure 2). Intramolecular cyclisation of *syn*-**4** could proceed either *via* transition state **9**, 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 **10** containing none of these destabilising interactions. Cyclisation of *syn*-**4** with ethoxy THF **5** should thus afford dihydropyran **14** possessing the undesired *cis*-22,26-relative stereochemistry. Similarly, *anti*-annelating agent **4** could react *via* the two possible transition-states **11** and **12**.

Steric compression between the $SiMe_3$ substituent and the C_{25} moiety should strongly disfavour **12** as compared to **11** in which such diaxal interactions are absent. ISMS cyclisation using *anti*-**4** should thus deliver

dihydropyran **15** possessing the correct *trans* relative stereochemistry between C_{22} and C_{26} of subunit **3**.

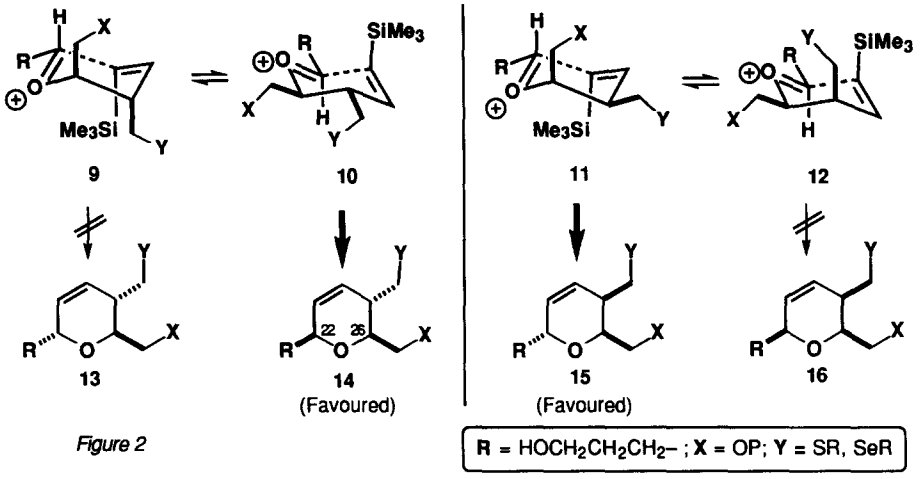


Figure 2

anti-Silylether **20** was readily prepared in three steps from (*E*)-3-hexene oxide **17** (Figure 3). Stereoselective ring opening of **17** using aluminium reagent **18** was followed by the addition of DIBAL to the C-C triple bond of **19** and protonation of the resulting vinylalane;[7-9] silylation then afforded the required annelating agent **20** in 50% overall yield. Pleasingly, ISMS condensation of silylether **20** occured in excellent yield to

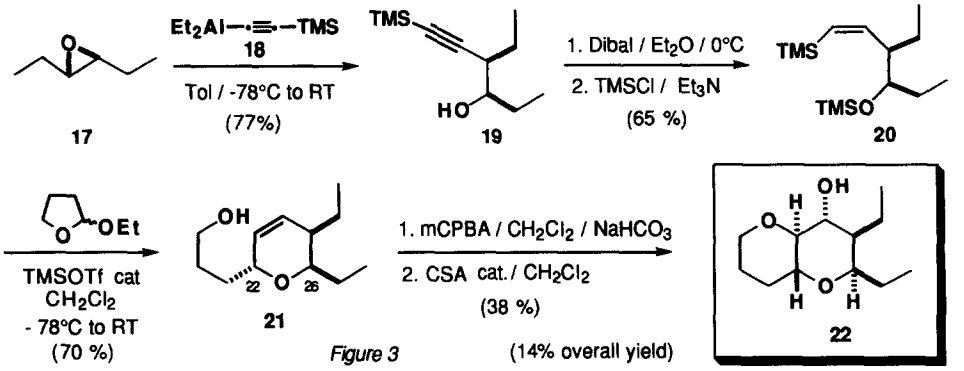


Figure 3

afford the single diastereoisomer **21**. The *anti*-relationship between the substituents at C_{22} and C_{26} was unambiguously established by X-ray diffraction analysis of derivative **23** (Figure 4).[10] The formation of *anti*-**21** supports our previous analysis and suggests the chair-like transition state **11** as the most probable one for the ISMS cyclisation of *anti*-**20**.

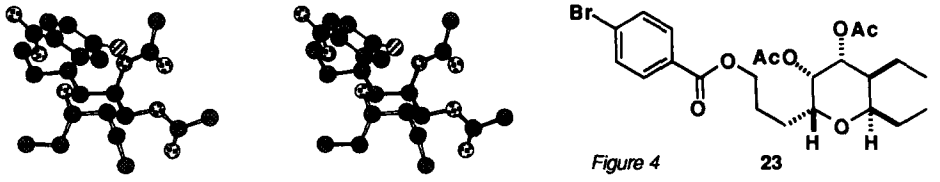


Figure 4

The completion of the synthesis of model *trans*-dioxadecalin **22** was expediently realised by stereoselective epoxidation from the α-face[11] followed by cyclo-etherification under acidic conditions.[12]

In summary, we have described a short and efficient route for the preparation of a variety of polysubstituted dihydropyrans. In particular, this methodology has enabled us to assemble, in only six steps, the bicyclic alcohol **22**, which contains all the structural motifs present in the middle portion **2** of okadaic acid. The synthesis of **2**, using the novel approach reported in this letter 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. AD is grateful to the Royal Society for a postdoctoral fellowship.

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6. This observation suggests that oxy-Cope rearrangement does not take place under these conditions.
7. Opening of this simple epoxide by trimethylsilyl alkynyl lithium under a variety of conditions failed to give **19**. Only the method of Yamaguchi afforded the desired homopropargylic alcohol **19**, albeit in a modest 30% yield. Yamaguchi, M.; Nobayashi, Y.; Hirao, I. *Tetrahedron*, **1984**, *40*, 4261.
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10. Compound **23** was prepared by esterification of the primary alcohol function of **21** followed by catalytic dihydroxylation (Van Rheenen, V.; Kelly, R.C.; Cha, D.F. *Tetrahedron Lett.*, **1973**, 1976) and exhaustive acetylation.
11. Epoxidation of **21** using mCPBA resulted in the sole formation of the α-oxirane. This selectivity probably results from the shielding of the β-face by the axial C_{26} susbtituent.
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(*Received in UK* 27 *February* 1997; *accepted* 7 *March* 1997)