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Application of a new nucleophilic addition/ring closure (NARC) sequence to the synthesis of enantiomerically-pure 2,8-dioxabicyclo[3.2.1]octanes of relevance to the squalestatins and zaragozic acids

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Abstract

A rapid method for the enantioselective construction of 2,8-dioxabicyclo[3.2.1]octanes of relevance to the zaragozic acids, employing a tandem NARC sequence of aldol and intramolecular Wacker reactions, is described.

The zaragozic acids (or squalestatins)[1,2] are fungal metabolites whose isolation and structural characterisation were reported independently by three groups in 1992.[3] These metabolites have attracted much interest[1–4] as they show picomolar inhibition of the enzyme *squalene synthase* (EC 2.5.1.21), the first committed step in the biosynthesis of sterols. Hence they have been identified as excellent lead drugs in the development of new anti-hypercholesterolaemic agents.[1–4] However, to date these natural products have not been successfully developed into a useful chemical therapeutic agent. One reason for this is the lack of rapid means of assembling, enantioselectively, the unusual 2,8-dioxabicyclo[3.2.1]octane core[5–24] (see Fig. 1).

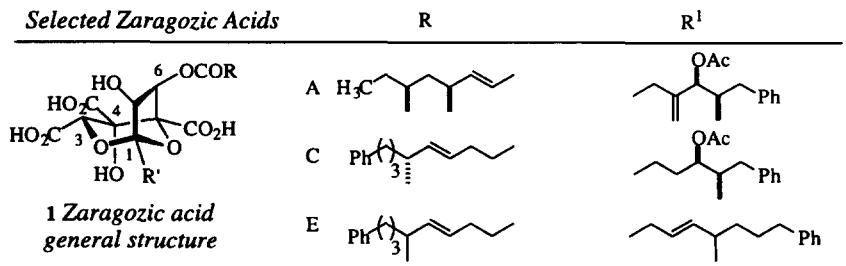

Figure 1.

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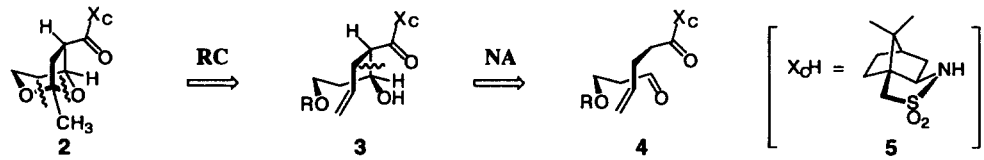
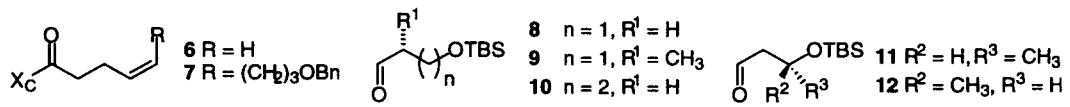
Recently, we highlighted the value and potential of the use of NARC sequences in the stereoselective synthesis of complex heterocycles.[25] In this approach, heterocycles are formed by a sequence of nucleophilic addition followed by ring closure. This approach has been used by us and others to prepare heterocycles found in a variety of important natural products including, to name a few, nonactic acid,[26] the pamamycins[27] and X-206.[28] As part of a program directed towards the development of a general approach to the synthesis of libraries of zaragozic acid analogues, we report in this letter the successful application of a new NARC sequence[25] to a new enantioselective synthesis of selectively substituted 2,8-dioxabicyclo[3.2.1]octanes. Our retrosynthetic analysis is shown in Scheme 1.

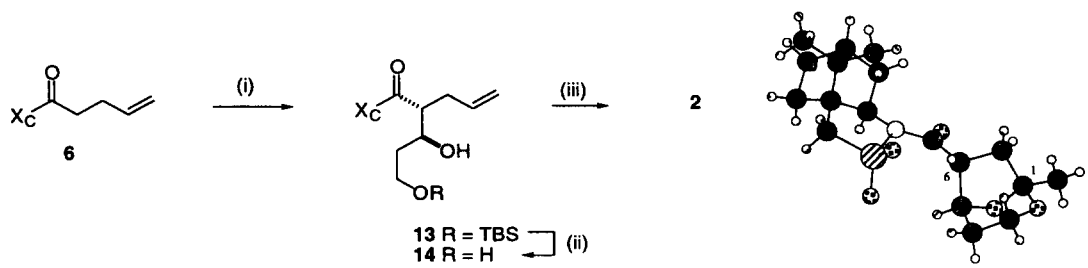


Scheme 1. Retrosynthetic analysis of the 2,8-dioxabicyclo[3.2.1]octane core

We envisaged the nucleophilic addition (NA) to be an asymmetric aldol reaction[29] and the ring closure (RC) to be an intramolecular Wacker process.[30–32] In this letter we focus on the enantioselective synthesis of the 2,8-dioxabicyclo[3.2.1]octane skeleton and the inclusion of substituents at different locations around the molecule. Substrates, **6** to **12**, for the NARC sequences were prepared by standard methods.



Asymmetric aldol coupling[29,33] of **6** with aldehyde **8** provided the partially protected enediol **13** as a single stereoisomer (Scheme 2). Since only free diols had been employed previously in the intramolecular Wacker process we first desilylated **13** using conc. HCl in THF.[34] Subsequent treatment of diol **14** under typical Wacker conditions ($PdCl_2$ (catalytic), $CuCl_2$, O_2)[30] provided the bicyclic product **2** in good yield. Conclusive evidence for the structure of **2** was provided by its X-ray crystal structure (Scheme 2).

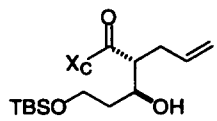
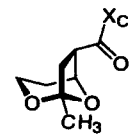
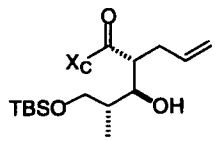
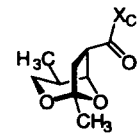
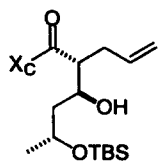
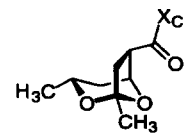
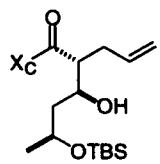
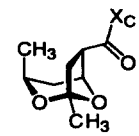
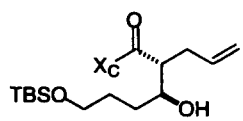
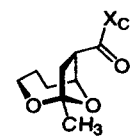
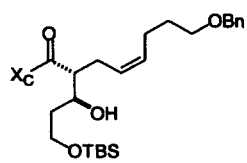
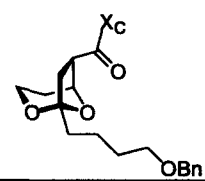


Scheme 2. (i) (a) Et_2BOTf, $Et_2(i\text{-}Pr)N$, CH_2Cl_2 (b) **8**, 95%; (ii) conc. HCl/THF (1:10), rt, 74%; (iii) $PdCl_2$ (5 mol%), $CuCl_2$, DME, O_2, 65°C, 12h, 60%

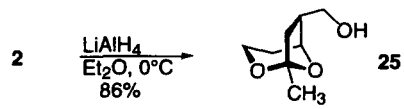
Direct ring closure of mono-silyl ether **13** proceeded as efficiently as that for **14**, obviating the need for desilylation prior to ring closure. Presumably the HCl generated during the Wacker oxidation is sufficient to promote desilylation of the primary silyl ether. (The remarkable stability of bicyclic acetals of this type to acidic conditions is well-precedented.[1])

With these results in hand we coupled **6** to aldehydes **8–12** and **7** to **8** (see Table 1). All these aldol reactions proceeded with essentially complete diastereoselectivity. Each of the adducts was then subjected to the ring closing conditions described above. In each case the bicyclic product was produced in good yield. Significantly, this process was successful with secondary as well as primary silyl ethers (entries 3 and 4) allowing the introduction of substituents at C3 and C4. Most important, ring closure

Table 1
Results from NARC sequences

Entry	Reactants	Aldol adduct		Yield (%)	Ring Closed Product		Yield (%)
1	**6 + 8**		**13**	95		**2**	60
2	**6 + 9**		**15**	94		**16**	60
3	**6 + 11**		**17**	95		**18**	65
4	**6 + 12**		**19**	94		**20**	50
5	**6 + 10**		**21**	56		**22**	91
6	**7 + 8**		**23**	71		**24**	39

of the internal alkene **23** was also successful (entry 6) although in relatively modest yields. This last example, which is not optimised at this stage, provides access to 2,8-dioxabicyclo[3.2.1]octanes bearing functionalised substituents at C1, which should be of great value in the design and synthesis of zaragozic acids and their analogues. To the best of our knowledge this is also the first example of an intramolecular Wacker oxidation of an *internal* alkene.[35] (No evidence was obtained for the formation of isomeric structures from reaction at the more remote locus of the internal double bond.) This process also succeeded with aldehyde **10** providing the first such 2,9-dioxabicyclo[4.2.1]nonane **22** (entry 5) in excellent yield. Reductive removal of the auxiliary is straightforward, providing, for example, primary alcohol **25** again in excellent yield (Scheme 3). The results from the application of this method to the preparation of more highly functionalised derivatives will be reported shortly.



Scheme 3.

Acknowledgements

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