About the use of molecular workbenches and platforms in organic synthesis*

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Abstract: The concept of molecular workbenches is introduced. These workbenches are rigid templates onto which the substrate is fixed covalently and is thus arranged in a conformationally defined way. The workbench may be disconnectible (i.e. after the functionalization of the substrate it is removed by bond cleavage) or non-disconnectible. In this case the workbench is irreversibly incorporated into the target structure. This concept is illustrated by additions to (E) olefins (disconnectible workbench) and a synthesis of dihydrocodeinone (non-disconnectible workbench).

INTRODUCTION

The concept of molecular workbenches (ref.1) is introduced and outlined in Fig. 1. According to the distinction between disconnectible and non-disconnectible workbenches this account falls into two sections, the first one describing the application of auxiliary like disconnectible workbenches in the functionalization of double bonds, and the second one the incorporation of a non-disconnectible workbench into the ultimate target structure (dihydrocodeinone) at a very early stage of the total synthesis.

Definition of Molecular Workbenches

-Disconnectible
 and nondisconnectible workbenches:
-Arrays of rigid substructures
 (e.g. aromatic or heterocyclic systems)
-chemically relatively inert
-high force constants regarding
 vibration and deformation

Fig. 1. Definition of molecular workbenches

DISCONNECTIBLE WORKBENCHES

The idea to construct such workbenches (ref.1) occurred to us in connection with the dihydroxilation or epoxidation of an acyclic *(E)*-olefinic polyol such as **1** which gave unselective reaction to **2/3**-mixtures in the unmodified version (Fig. 2).

The synthetic problem to solve was the stereoselective dihydroxylation of

AD-mix and OsO₄ gave
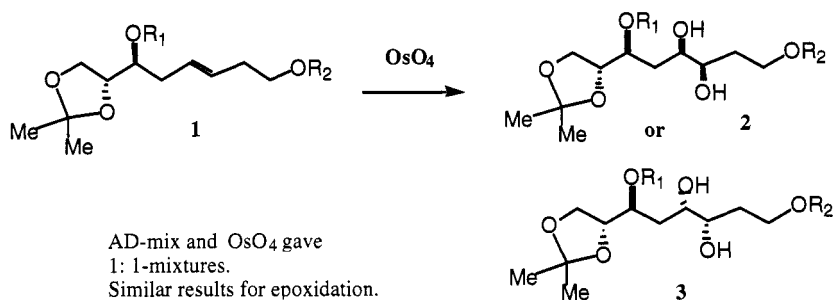1: 1-mixtures.
Similar results for epoxidation.

**Fig. 2** Unselective additions to acyclic (E) olefins.

Therefore, it was decided to incorporate the acyclic olefin into a cyclic template (= workbench) by using the terminal functions as anchoring groups. The next poblem to solve was the helicameric inversion which was to be expected from cyclic (E)-olefins with ring sizes of >8 carbons (Fig. 3). A possible solution to this problem was envisaged in form of the ansa macrolide template which should slow down helicameric mobility and, at the same time, exert diastereofacial shielding of the double bound by virtue of the benzenoid ring (Fig. 4). Thus, the ansa chain **4** was prepared by routine methods and connected to the commercially available benzenoid platform **5**. After chromatographic separation of the anomers **6** the ansa macrolides **7** and **8** were obtained by macrolactonization and analyzed by single crystal diffraction (Fig.s 8a/b). It turned out that the configuration of the acetal center determines the helicity of the ansa olefin (Fig. 6) and that the attack of the reagents (osmium tetroxide or m-chloroperbenzoic acid) occurred from the outside with varying selectivities. The stereoselectivity was dramatically increased for the 12-membered ring and the *trans*-acetal, whereas it was nonexistent for the 13-membered macrolide (Fig. 6). This means that there must be a very close fit between ansa chain and platform, similar to the one in enzyme and substrate. Even an increase by one carbon atom in the ansa chain is intolerable for a stereoselective addition! Another issue was the conformational rigidity of the workbench during the addition. To this end the crystal structures of olefin **7** (R=Bn, n = 1) and ist epoxide were superimposed to show only minimal discrepancies (Fig. 9). This indicates a significantly high geometrical stability of the molecular workbench as postulated in Fig. 1.

How to slow down inversion of larger rings ?
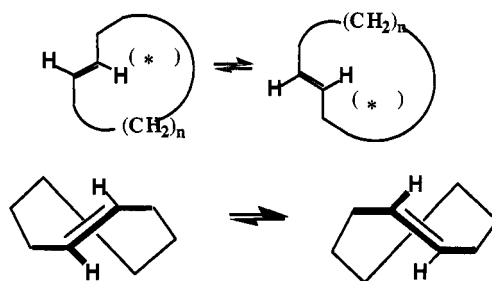
1. The smallest possible ring is of size 8 (too small for ansa compound ?)

2. in the 8-membered ring the helicamer inversion is slow

 (required temperature ca. 150 °C)

3. larger rings show rapid helicamer inversions

 (9-membered ring already at 0°C!)

Fig. 3. Helicameric mobility in cyclic (E) olefins
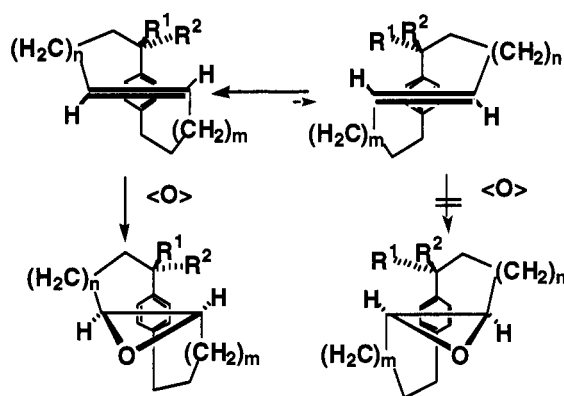
high selectivity

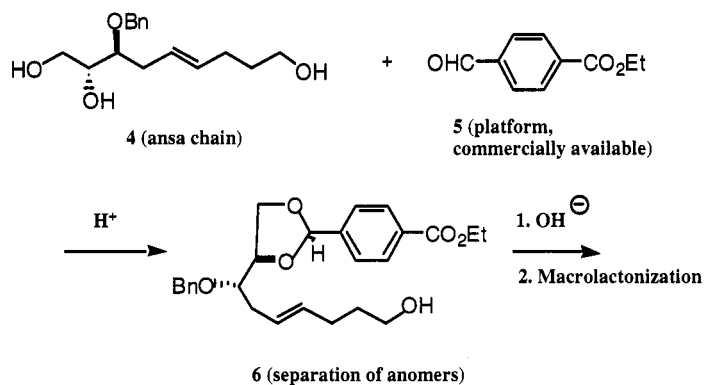**Fig. 4.** Concept of ansamacrolides as chiral molecular workbenches

4 (ansa chain)

5 (platform, commercially available)

6 (separation of anomers)

Fig. 5. Synthesis of the chiral workbench

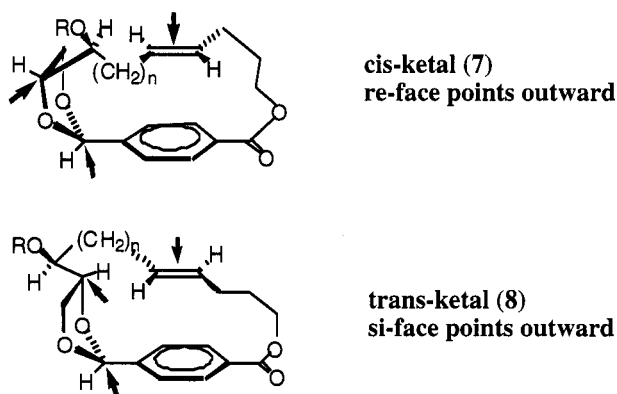**Ansamacrolides : n =1 and 2, R = Bn and Me (60-70% Yield) The acetal center determines the helicity of the olefin**

cis-ketal (7) re-face points outward

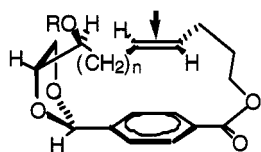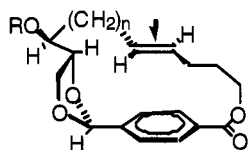**trans-ketal (8) si-face points outward**

Fig. 6. Helicity of the ansamacrolides **7** and **8**

Selectivities for Epoxidation (mCPBA) (A)
and Dihydroxilation (OsO₄/NMO) (B)

ring size = 12
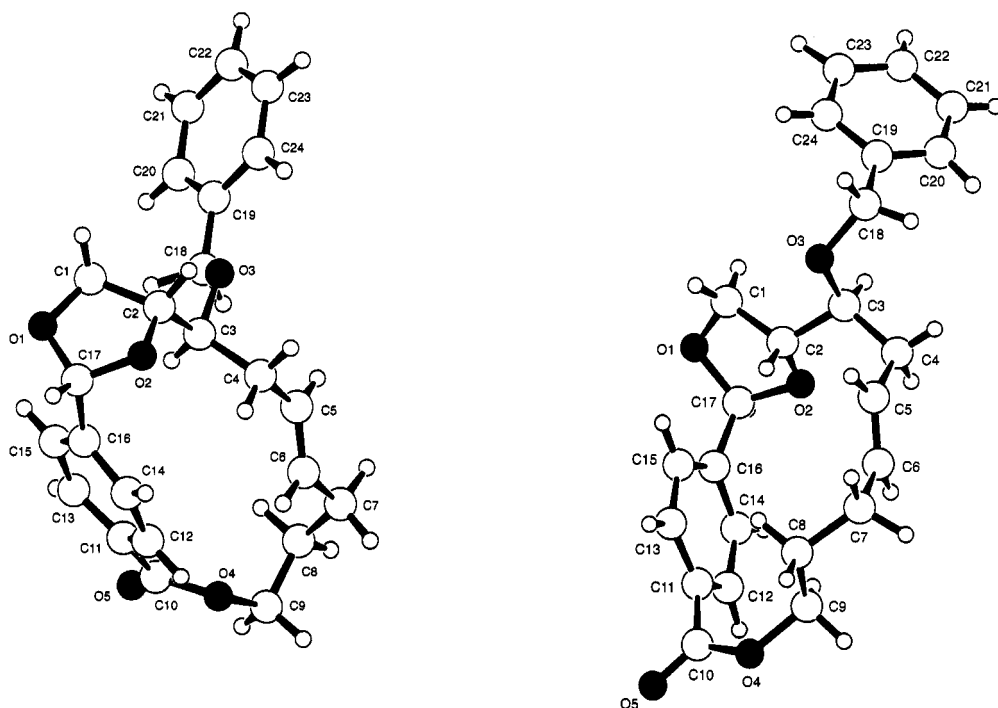*A 90 : 10   B > 95 : 5*

ring size = 13
A   2 : 1   B 1.5 : 1

ring size = 12
A > 98 : 2   B > 99 : 1

ring size = 13
A 1.5 : 1   B 1.5 : 1

Platform and ansa chain must be adjusted to one another
(like enzyme and substrate)

Fig. 7. Selectivities of the double bond additions

Fig. 8a. Crystal structure of **7** (n = 1, R = Bn)

Fig. 8b. Crystal structure of **8** (n = 1, R = Bn)

To disconnect the workbench after the functionalization of the double bond hydrogenolysis of the benzylic
CO-bonds was employed to furnish polyol **10** from precursor **9**. In the case of the epoxide **11**
hydrogenolysis was combined with an S_N2-type cyclization to generate the tetrahydrofuran derivative **12**

stereoselectively. The p-methylbenzoate served as a protective group for one of the primary OH-functions which could easily be differentiated from the second primary OH-group (Fig. 10).

Contrary to this approach which uses chiral ansa chains and an achiral platform, a second approach was tested with achiral ansa chains and chiral platforms (Fig. 11). In fact similar selectivities were observed as before, the best results being obtained for 12-membered rings and trans-acetals (Fig. 12). For instance the epoxidation of olefin **14** proceeded with >98% dr. The removal of the chiral platform was again achieved by catalytic hydrogenolysis.
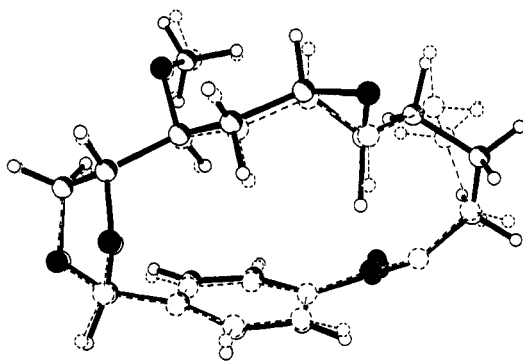

Fig. 9. Superimposition of the crystal structures of olefin **7** (R = Me, n =1, empty circles) and its epoxide (black circles)

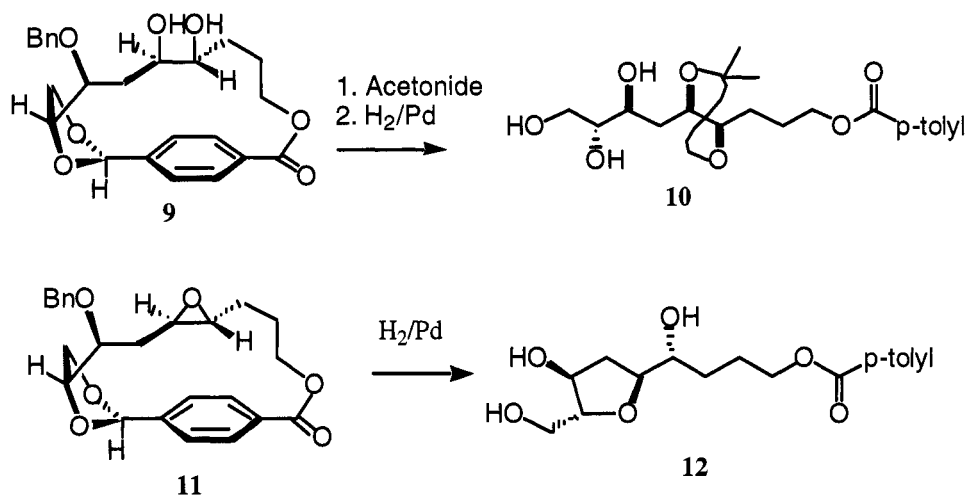**Fig. 10.** Removal of the platform by hydrogenolysis
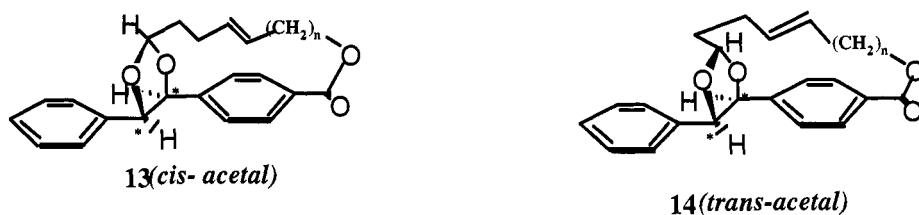
Chiral Platform + Achiral Ansa Chain

13(cis- acetal)

14(trans-acetal)

Helicity is independent of the acetal geometry

Fig. 11. Chiral workbenches from chiral platform and achiral ansa chain

mCPBA/ CHCl₃/-30°C

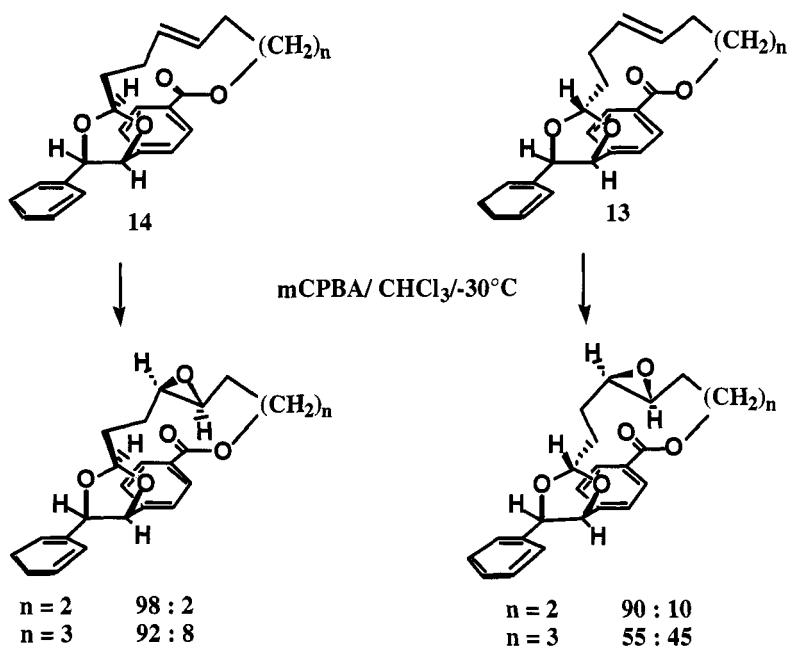| n = 2 | 98 : 2 | | n = 2 | 90 : 10 |
| n = 3 | 92 : 8 | | n = 3 | 55 : 45 |

Fig. 12 Selectivities for chiral workbenches with achiral ansa chains

NON-DISCONNECTIBLE CHIRAL WORKBENCHES

This approach is illustrated by the synthesis of morphinane alkaloids (e.g. dihydrocodeinone, **22**) which uses phenanthrenone **15** as a chiral platform on which the remaining two rings are mounted successively (Fig. 13)[2,3]. In this way all stereoproblems are easily solved, as the rigid platform serves quite well as a template for the further construction of the molecular framework. One of the key steps is the diastereocontrolled 1,4-addition of an anionic synthon to **15** to establish the benzylic quaternary center and to construct the characteristic piperidine ring in **22.**
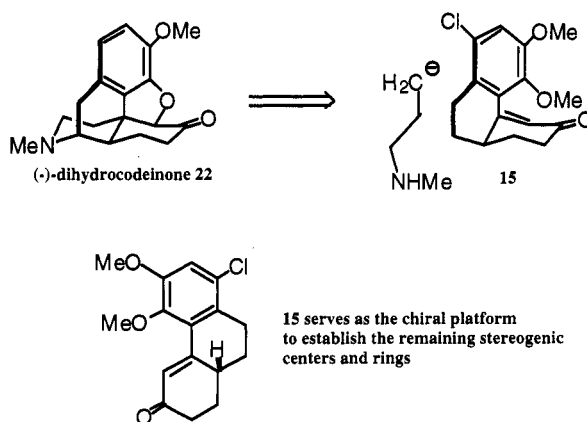
Fig. 13. Phenanthrenone 15 as a non-disconnectible workbench for the synthesis of 22

ACKNOWLEDGEMENT

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3. D.Trauner, S.Porth, T.Opatz, J.W.Bats, G.Giester and J.Mulzer, Synthesis:653-664(1998).