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Ansa macrolides as molecular workbenches for stereoselective additions to achiral (*E*) olefins

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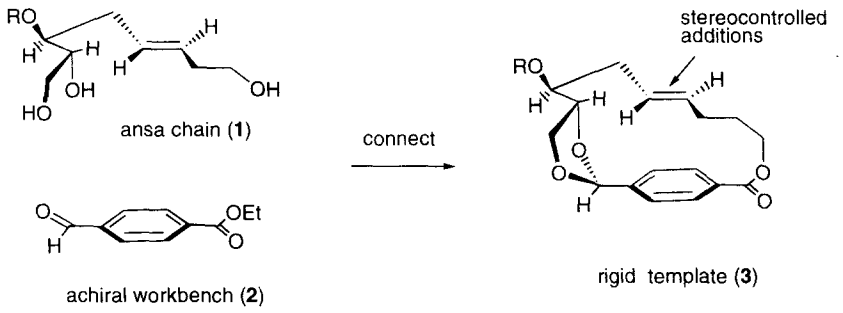
Abstract:

Highly stereocontrolled additions to achiral acyclic (*E*) olefins are achieved via incorporation into an ansa macrolide with a non-racemic stilbene diol (molecular workbench approach).

Keywords: ansa compounds; addition reactions; macrolides; stereocontrol

Recently we described the concept of molecular workbenches (Scheme 1). In this approach, a chiral ansa chain **1** containing an (*E*) olefin was connected with an achiral workbench **2** to form an ansa macrolide **3** which acts as a rigid template for stereoselective additions to the double bond [1]. After the addition ansa chain and workbench were disconnected.



Scheme 1

In this Letter we report the extension of this concept to the combination of an **achiral** (*E*) olefinic ansa chain and a **chiral** workbench and show that high asymmetric induction is provided from the workbench during epoxidation and dihydroxylation of the double bond. The synthesis of the workbench **6** (Scheme 2) started with the Wittig olefination of the commercially available aldehyde **4** to give **5** which was converted into enantiomerically pure diol **6** via a Sharpless AD-reaction [2]. The synthesis of our model ansa chains **11** and **12**

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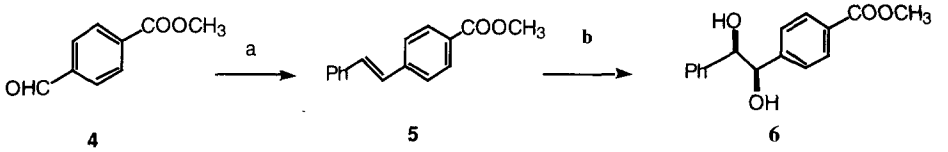
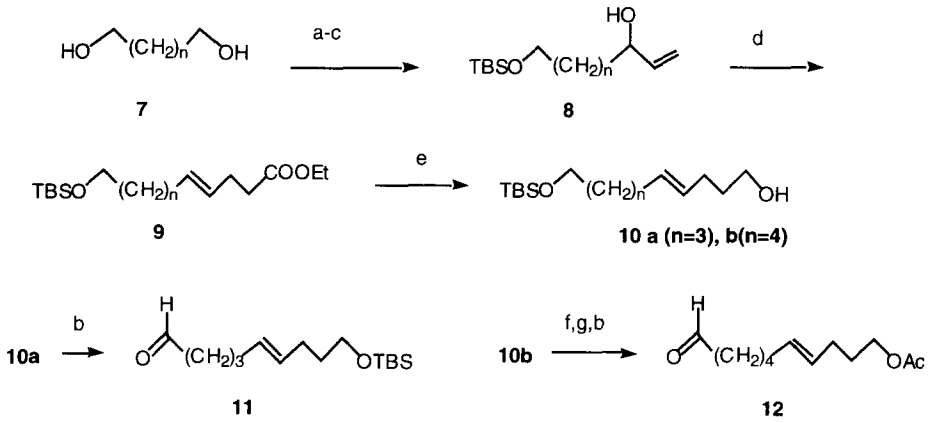
(Scheme 3) made use of a Johnson-Claisen rearrangement of allylic alcohol **8** to ester **9** to ensure exclusive (*E*) olefin formation. Ansa chains **11/12** and workbench **6** were connected (Scheme 4) by stereouncontrolled acetal formation followed by hydroxyl and carboxyl deprotection and Yamaguchi [3] or Keck [4] macrolactonization to form the olefinic phanes [5] **13a/b** as a mixture of *cis-/trans*-stereoisomers which were separated by chromatography.



4 5 6

a. $BnPPh_3Cl$,NaOMe,MeOH,then hv, >95%(E),78%. b.Sharpless-AD-mix-β, 91%, >99.5% ee

Scheme 2



7 8 9 10 a (n=3), b(n=4) 11 12

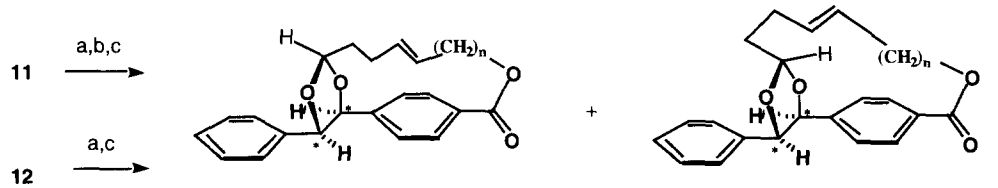
a. $Me_2tBuSiCl/NEt_3$/DMAP/THF/82%. b. oxalyl chloride,NEt_3,DMSO,90%. c. CH_2=CHBr,Mg,THF,92%. d. $MeC(OEt)_3$,$MeCO_2H$,toluene,reflux,91%. e.LAH,Et_2O,86%. f. Ac_2O, pyridine,94%. g.NBu_4F,THF,93%.

Scheme 3

All four macrolides were crystalline and could be characterized by single crystal diffraction [6] (Figure 1). It can be easily seen that the olefinic plane in *trans*-**13a/b** is roughly coplanar with the 1,4-bridged benzenoid ring, whereas the olefin in *cis*-**13a/b** is tilted. The helicity of all four macrolides is the same and, hence, independent of the configuration at the acetal center so that in all cases the *re,re*-face of the olefin points outwards. To probe the diastereoselectivity of double bond additions epoxidation and dihydroxylation were used (Scheme 5, Table 1, major diastereomers were isolated by chromatography).

The structure of the addition products was examplarily determined by single crystal diffraction [6] of epoxides **14b** and **16b**. From these structure it was concluded that analogously to the former [1] cases the attack of the reagents occurs preferentially from the less hindered, outward face. From comparison of Figure 1 and the data in Table 1 it follows

that high stereoselectivity is observed only in those cases where the double bond is effectively shielded by the rest of the molecule, in particular the benzenoid ring. Thus, the selectivities of *trans*-**13a/b** are substantially higher than those in *cis*-**13a/b**, and it follows that the geometry of the acetal center and not so much the ring size determines the reactive conformation of the chain and hence the selectivity of the addition. As exemplified for diol **15b**, workbench and ansa chain may be easily disconnected by acetonide protection to form **18**, followed by ester reduction and hydrogenolysis of the benzylic positions to give **19** and **20** (Scheme 6).



a. +**6**, PPTS, toluene, reflux, >85%. b. KOH, aliquat™ 336, 95%. c. 2,4,6-trichlorobenzoyl chloride, NEt_3, DMAP, toluene, reflux, (cis-**13a** 45%, trans-**13a** 22%), or DCC, DMAP-hydrochloride, chloroform, reflux, (cis-**13b** 51%, trans-**13b** 28%).

Scheme 4

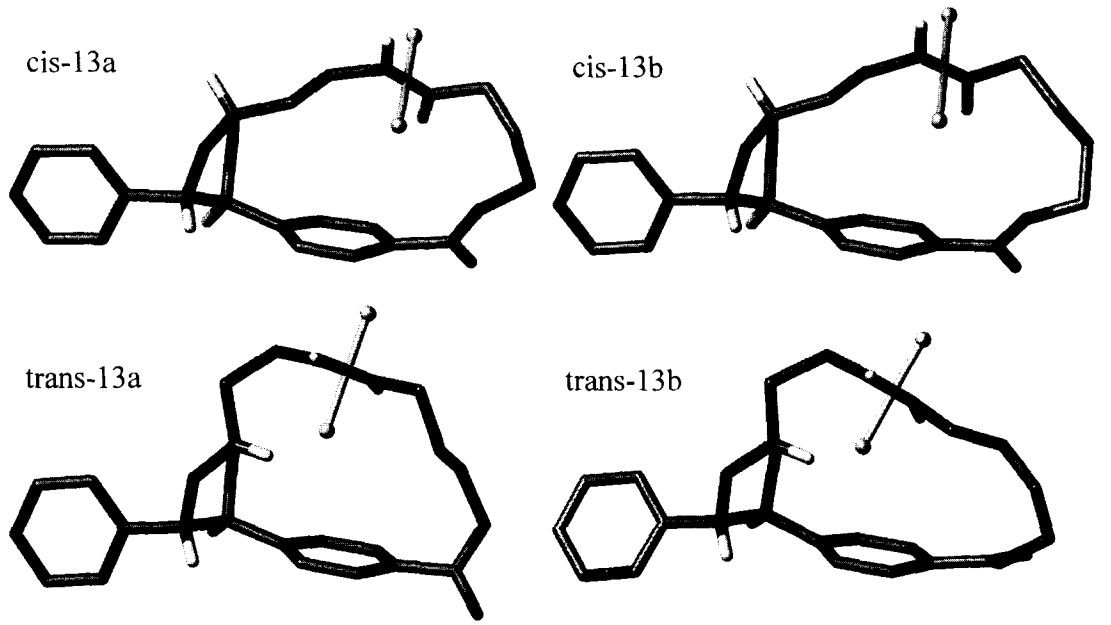
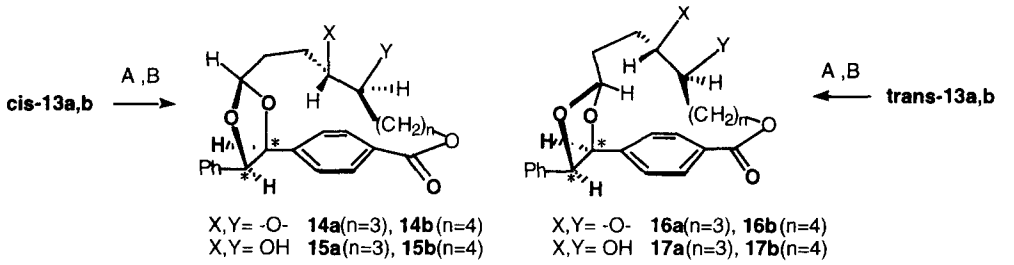


Figure 1.
Crystal Structures of *cis*- and *trans*-**13a/b** [7]



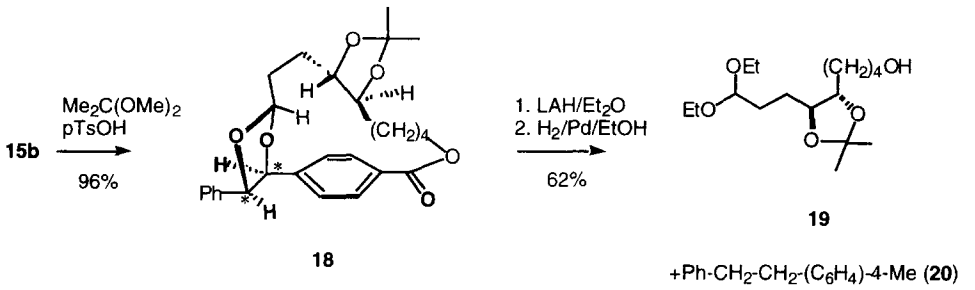
A. mCPBA, chloroform, -30°C. B. OsO_4, NMO, acetone-water, 0°C.

Scheme 5

Table 1.

Diastereoselectivity of Epoxidation and Dihydroxylation of *cis*- and *trans*-**13a/b**

educt	reaction	product	d.r.	combined yield (%)
cis-**13a** (n=3)	MCPBA	**14a** (n=3)	90:10	83
cis-**13a**	OsO_4	**15a**	75:25	91
cis-**13b** (n=4)	MCPBA	**14b** (n=4)	52:48	93
cis-**13b**	OsO_4	**15b**	59:41	90
trans-**13a** (n=3)	MCPBA	**16a** (n=3)	92:8	89
trans-**13a**	OsO_4	**17a**	>99:1	93
trans-**13b** (n=4)	MCPBA	**16b** (n=4)	92:8	95
trans-**13b**	OsO_4	**17b**	85:15	89



Scheme 6

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[5] First example of an ansa olefin : Noble KL, Hopf H, Ernst L. Chem Ber 1984,117:455-473.

[6] Crystallographic data were deposited at the Cambridge Crystallographic Data Centre.

[7] Crystal structures drawings were created with WebLab™ViewerPro™ v3.10 (Molecular Simulations Inc.).