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Diastereoselective formation of cyclochiral amino acids-substituted resorcin[4]arenes

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Abstract—The Mannich reaction between selectively tetratosylated resorcin[4]arene, formaldehyde and (*S*)-phenylalanine (or (*S*)-phenylglycine) methylamide gave cyclochiral mono- or dibenzoxazines with high diastereoselection as revealed by NMR and X-ray structural studies. X-ray structures of the products show the variety of intramolecular interactions that can be responsible for the diastereoselection of this acid-catalyzed reaction.

Selectivity in thermodynamically controlled reactions relies on pronounced stabilization of the products. Such stabilization can be achieved via the favourable intramolecular interactions within the product molecule or through intermolecular interactions with other molecules (guests). A spectacular example of an intramolecular interaction driven reaction involves regioselective formation of tetrabenzoxazines from resorcin[4]arenes **1** through the Mannich reaction.[1] It has been shown that C_4 symmetrical tetrabenzoxazines are formed selectively among the many possible regioisomers due to the presence of four intramolecular hydrogen bonds. The process of benzoxazine ring closing/opening proved to be reversible under slightly acidic conditions.[2,3]

For modified resorcinarenes, for example, selectively tetratosylated **2**, the Mannich reaction is only possible at the two distant positions. Thus, the reasons for regioselectivity are more elusive and, in principle, both regioisomers are possible which have in fact, been observed.[4]

Resorcinarene benzoxazines are cyclochiral[5] even if no chiral amine or chiral auxiliary is used in the reaction. A racemic mixture containing cycloenantiomers can be separated using chiral HPLC.[2] Recently, it has been shown that by using simple chiral amines it is possible to induce cyclochirality in resorcin[4]arenes with reasonable diastereoselection.[3,6]

In this letter, we report on the diastereoselective Mannich reactions of tetratosylated resorcin[4]arene **2** with amino acid methylamides. We expected that additional non-covalent interactions within or between peptide-type fragments would allow for more controllable diastereoselectivity. Additionally, we were interested in using those multiple-binding-site cyclochiral products as potential receptors for chiral recognition. To the best of our knowledge, amino acid derivatives bearing primary amine functions have not previously been used in this type of reaction. The use of prolinol, which is a secondary amine, and does not form a benzoxazine product has been reported (cyclochirality was later introduced via closing a bora-heterocyclic ring).[7]

Selectively tetratosylated resorcinarene **2** was synthesized according to a known procedure in 15% yield (Scheme 1).[8] Then, **2** was subjected to Mannich reaction with formaldehyde and amines **3** or **4** (Scheme 1, Table 1). The previously reported typical conditions for this reaction are: methanol as a solvent, acetic acid (optional) and room temperature. Acetic acid plays a double role: as a catalyst for product formation and also as a catalyst for equilibration between the two possible cycloepimers. However, in our case the reaction of **2** with **3** or **4** under the above conditions resulted in recovery of the starting material even after a long reaction time. Reflux was required for the reaction to proceed

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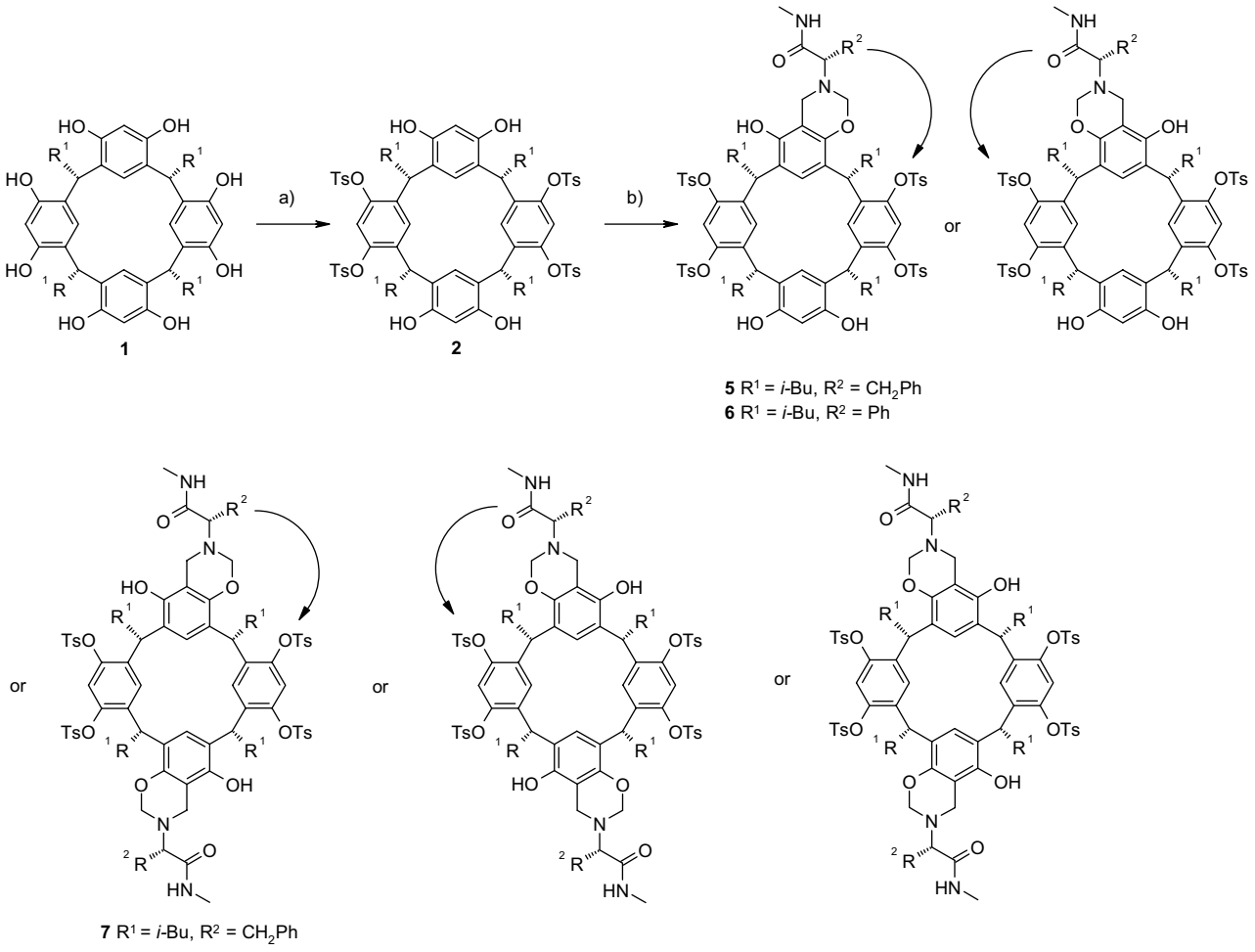

Scheme 1. Synthesis of chiral resorcin[4]arenes: Reagents and conditions: (a) TsCl, Et_3N, MeCN, 15%; (b) $HCHO_{aq}$, AcOH, amine (conditions see Table 1)—all the possible products are presented.

Table 1. Synthesis of the cyclochiral resorcin[4]arenes via Mannich reaction (Scheme 1)

Entry	Substrate	Conditions	Product	Yield (%)
1	(*R*,*S*)-Phenylalanine methylamide *rac*-**3**	MeOH, reflux 5 min, then 12 h, rt	*rac*-**5**	83
2	(*R*,*S*)-Phenylalanine methylamide *rac*-**3**	Dioxane, rt, 5 d, then precipitate with MeOH	*rac*-**5**	91
3	(*S*)-Phenylalanine methylamide **3**	MeOH, reflux 3 h, then 12 h, rt	**7**	83
4	(*R*,*S*)-Phenylalanine methylamide *rac*-**3**	MeOH, reflux 3 h, then 12 h, rt	*rac*-**7**	53
5	(*S*)-Phenylglycine methylamide **4**	Dioxane, rt, 5 d, then precipitate with MeOH	**6**	62
6	(*S*)-Phenylglycine methylamide **4**	MeOH, reflux 3 h, then 12 h, rt	**6**	68

due to the very poor solubility of **2** in cold methanol. In the case of using (*R*,*S*)-phenylalanine methylamide, *rac*-**3**, cooling the reaction after 5 min of reflux (Table 1, entry 1) resulted in the formation of a precipitate, which turned out to be monobenzoxazine *rac*-**5** (83% yield). Careful analysis of the 2D NMR spectra of this product revealed that we obtained a single cycloisomer (in racemic form). The same monosubstituted cycloisomer *rac*-**5**, was obtained when the reaction was carried out in dioxane at rt, *rac*-**5** was precipitated with methanol (entry 2). Attempts to obtain pure optically active **5** failed due to purification problems, even though TLC indicated that the product was formed in reasonably high yield. The X-ray structure of *rac*-**5** (Fig. 1) indicates that taking into account the natural (*S*)-enantiomer of phenylalanine clockwise or P (assuming that the lower rim of the resorcin[4]arene is the bottom of the molecule and looking from the inside of the cavity) isomer in the boat conformation was obtained. The phenylalanine arm is involved in an intramolecular hydrogen bond across the molecule, that is, the carbonyl oxygen atom interacts with the phenolic OH group from the opposite aromatic ring. Additionally, each phenylalanine fragment adopts such a conformation so that the amide hydrogen atom can interact with the free electron pair of the amino groups. The phenylalanine CH_2 group is located in the pocket formed by the oxygen atoms and the horizontal resorcinarene ring.

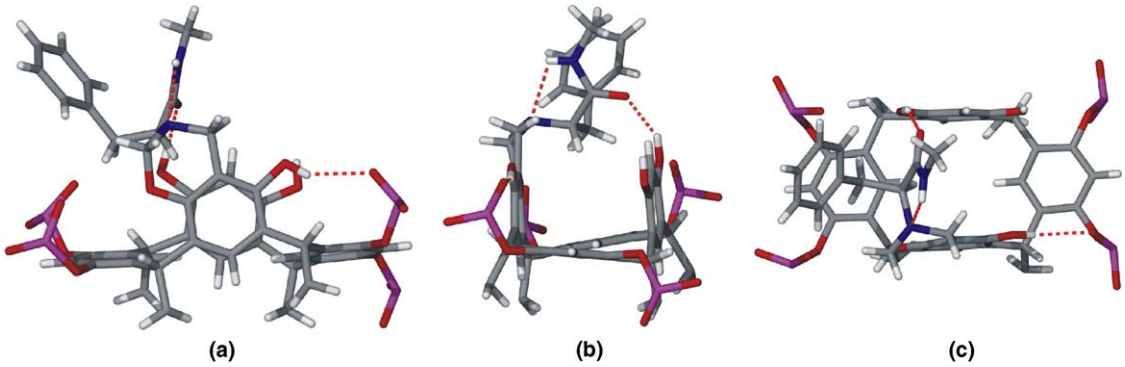

Figure 1. X-ray structure of *rac*-**5**: tosyl group, lower rim aliphatic chains and solvent are removed for clarity. (a) Side view: C—gray, H—white, O—red, N—blue, S—purple; (b) side view, 90° rotation; (c) top view.

Formation of the dibenzoxazine product required longer heating times in methanol (1–3 h, entry 3). Under such conditions, the reaction gave selectively, and with a high yield **7** (83%) as the only product. The product is reasonably stable and its NMR spectra did not show epimerization even after a few days in commercial $CDCl_3$. It is noteworthy that in the case of using the racemic substrate (*R*,*S*-phenylalanine methylamide, *rac*-**3**) under the same condition as for the formation of dibenzoxazines the only isolable product was the same as in the case of using optically pure substrate except that the material is racemic (entry 4, *rac*-**7**). No mixed products were isolated.

^1H and ^{13}C NMR spectra of product **7** show only half of the maximum number of signals suggesting formation of a single diastereoisomer having C_2 symmetry. Accidental overlap of the signals for two possible diastereoisomers of that symmetry (with clockwise or anticlockwise ring closure) has been excluded on the basis of acid-induced epimerization experiments (see Supp. data). Addition of acetic acid to a $CDCl_3$ solution of **7** led after seven days to a second set of signals, which also showed only half of the maximum number of signals. The second set of signals were assigned by 2D COSY and indicated the formation of the second C_2 diastereoisomer, having both benzoxazine rings closed in the opposite direction.

The X-ray structure of product **7** (Fig. 2) confirmed the C_2 symmetry and additionally allowed for determination of the direction of induction. Again clockwise or P diastereoisomer in a boat conformation was obtained. The hydrogen bonding pattern found in monobenzoxazine **5** is also retained (and doubled) in the case of di- benzoxazine **7**, that is, each of the phenylalanine arms is involved in an intramolecular hydrogen bond across the molecule, and the amide hydrogen atom interacts with the free electron pair of the amino groups. It is quite unusual that the macrocyclic ring of the parent resorcin[4]arene adopts a considerably distorted boat conformation. The two aromatic rings with amino acid arms remain parallel but their main axes are twisted by 33.3° to each other. The other two aromatic rings (the tosylated ones) are also twisted—in a propeller-like way. The reason for this high distortion is due to steric overcrowding at the upper rim (Fig. 2).

In the case of the Mannich reaction with (*S*)−phenylglycine methylamide **4** (entries 5 and 6), despite many efforts only monosubstituted product **6** could be obtained in a maximum yield of 68%. The high-resolution NMR spectrum of **6** indicated that the product obtained was a single diastereoisomer. Surprisingly, the X-ray quality crystal of **6** (Fig. 3) exhibited a centrosymmetric P-1 space group, which meant that this particular crystal was a racemate. We believe that minor partial racemization might have taken place during the synthesis or crystallization stage, since the sample examined had been subjected to many crystallization attempts, and we were

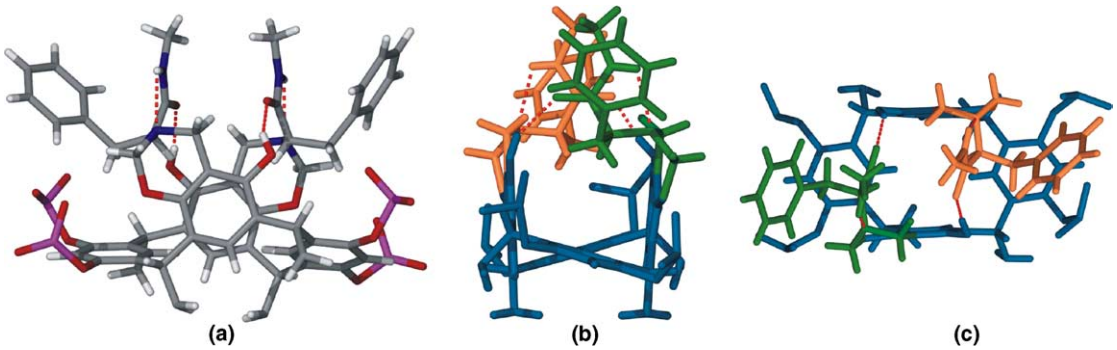

Figure 2. X-ray structure of **7**: tosyl group, lower rim aliphatic chains and solvent are removed for clarity. (a) Side view: C—gray, H—white, O—red, N—blue, S—purple; (b) side view, 90° rotation, resocin[4]arene skeleton—blue, arm 1—green, arm 2—orange; (c) top view.

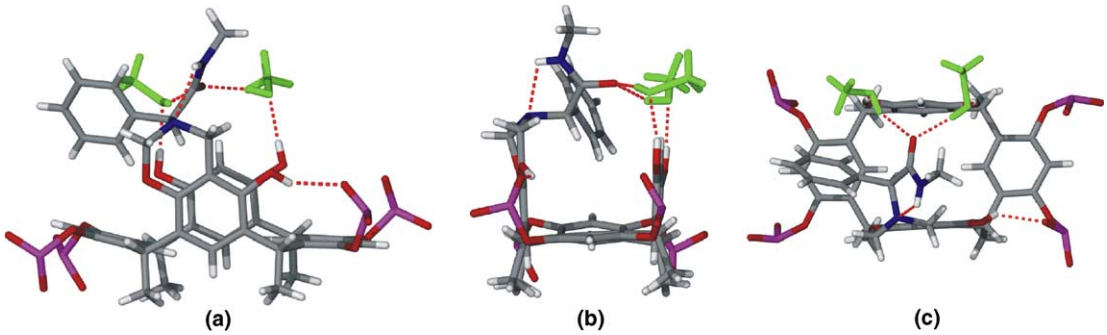

Figure 3. X-ray structure of *rac*-**6**: tosyl group and non-interacting solvent molecules are removed for clarity. (a) Side view: methanol—green, C—grey, H—white, O—red, N—blue, S—purple; (b) side view, 90° rotation of (a), (c) top view.

unable to grow crystals from the freshly prepared sample under analogous conditions. The X-ray structure of *rac*-**6** shows that taking into account the correct (*S*)-enantiomer of phenylglycine again, a clockwise (or P) cycloisomer was obtained. This was also in agreement with the CD spectra, which showed the same sign of the Cotton effect for **7** and **6** (see Supp. data). The macrocyclic ring of the parent resorcin[4]arene adopts a regular boat conformation. The carbonyl oxygen atom points in the direction of the central aromatic hydrogen atom on the opposite phenolic ring (O···H distance is 2.87 Å). Two methanol molecules serve as intermediaries in this interaction and form hydrogen bonds between carbonyl oxygen atoms and the two phenolic OHs. Again the phenylglycine fragment adopts such a conformation such that the amide hydrogen atom can interact with the free electron pair of the amino groups. Such a conformation is additionally stabilized by the face-to-edge interaction between the phenyl ring of phenylglycine and one of the horizontal resorcinarene rings.

In conclusion, X-ray analysis indicates that in all cases we obtained the same left-handed (or clockwise, P) cyclodiastereoisomer. The conformations and the interaction patterns of the amino acid arms for products **5**, **6** and **7** are also very similar: in all cases intramolecular hydrogen bonds $N_{amine}\cdots H\text{–}N_{amide}$ are present, hydrophobic side chains interact with aromatic horizontal resorcinarene rings and the carbonyl oxygen atom is involved in a hydrogen bond. Such interactions can sum-up to give considerable stabilization of the products and thus can be responsible for the high diastereoselectivity of this reaction.

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Supplementary data

Synthetic details, spectral characteristics (including CD spectra) and crystallographic details for the reported compounds have been deposited as supplementary material. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.08.113.

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