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All-cis Cyclopentane Scaffolding for Combinatorial Solid Phase Synthesis of Small Non-Peptide Compounds

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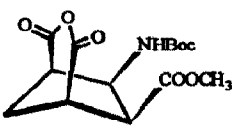
Abstract: A convenient synthesis of all-cis cyclopentane template **6** from commercially available anhydride **1** is described. Regioselective conversion of the anhydride **6** to functionalized cyclopentanes **7** with a range of nucleophiles, as well as the regiochemical assignment of the major regioisomer are also discussed.

Dramatic advances in combinatorial chemistry have revealed a high potential of generating a large diversity of relatively small, structurally defined organic molecules as conceivable drug candidates.[1,2] Furthermore, quite recently, non-peptidic templates have emerged from the realm of theoretically interesting molecules as useful components of biologically active compounds amenable to further optimization.[3-7] This concept has uniformly taken advantage of appreciable stereorigidity and adjustable architecture of properly chosen scaffolding elements.

As a part of our program on the synthesis of template based non-peptidic libraries, we report here the synthesis of racemic, all-cis substituted cyclopentane anhydride **6** as a key structural component of "small organic molecule" libraries as indicated by the general formula of **7**.



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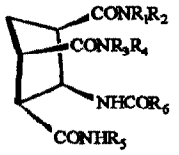

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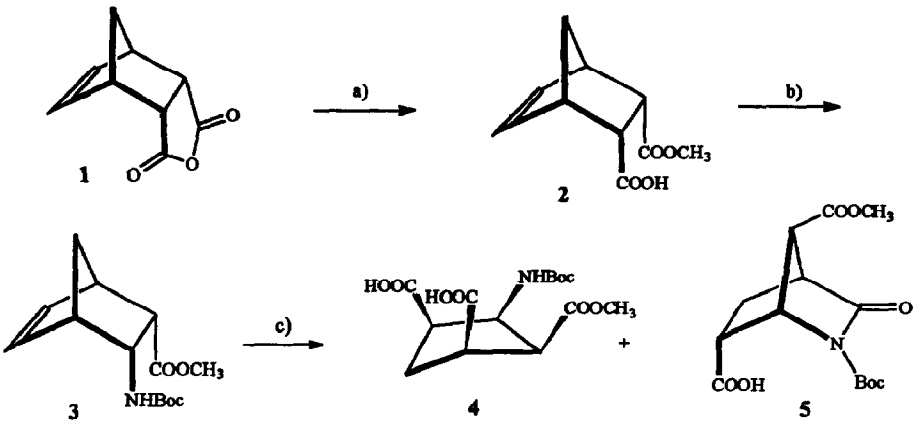
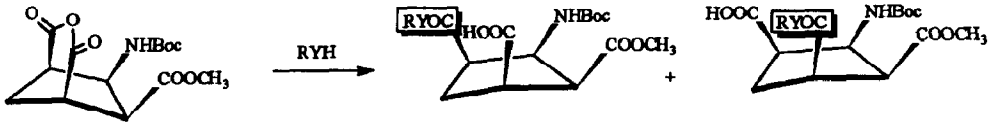
The strategic concept of the synthesis is outlined in Scheme 1. Starting from commercially available cis-5--norbornene-endo-2,3-dicarboxylic anhydride **1**, the racemic methyl ester **2** was prepared in 97% yield by reaction with methanol in the presence of tertiary base. Curtius rearrangement followed by amino group protection afforded, after crystallization, derivative **3** in 75% overall yield. Oxidation of the skeletal double bond using $RuCl_3/NaIO_4$ in CCl_4-CH_3CN-H_2O (2:2:3) provided all-cis substituted cyclopentane diacid **4** in 68% yield, accompanied by a small amount of substituted azanorbornanone **5**.[8] Finally, reaction of the diacid **4** with DCC in CH_2Cl_2 gave anhydride **6** in 95% yield. In our preliminary investigations, we examined a variety of nucleophiles, which included MeOH, C_6H_5OH, $BzlNH_2$, $MeNH_2$, and $(Me)_2NH$, in the transformation of **6** → **8** and surprisingly, in all cases, regioselectivity greater than 75:25 (**8A**:**8B**) was observed.[9] Confirmation of the geometry of the major product **8A**

Scheme 1



a) MeOH, NEt_3, Δ, 2h; b) 1. ClCOOMe, NEt_3, acetone, -10°C; 2. aq. NaN_3, workup; 3. dioxane, 90°C, 30min ; 4. aq. TFA; 5. aq. $NaHCO_3$/dioxane, $(Boc)_2O$; c) $RuCl_3$/ $NaIO_4$.

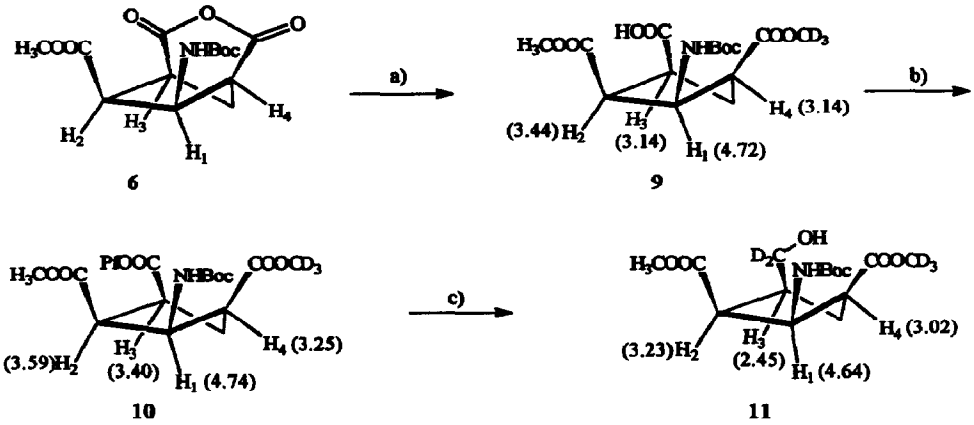
was provided indirectly by ^1H NMR homonuclear decoupling experiments. Since resonances of H-3 and H-4 protons in ^1H NMR spectra (centers of multiplets are given in parentheses - Scheme 2) were overlapping in region δ 3.1-3.2ppm ($CDCl_3$), the chemical correlation of the derived deuterated alcohol **11** was employed in the regiochemical assignment. The synthesis of alcohol **11** is shown in Scheme 2. Treatment of anhydride **6** with CH_2Cl_2 solution of CD_3OD (2 equiv) in the presence of NEt_3 provided diesters **8A,B** (RY = OCD_3) in 98% yield as a mixture of regioisomers (91:9). After crystallization, the major isomer **9** was transformed to pentafluorophenyl ester **10** in 95% yield using dicyclohexylcarbodiimide as a coupling reagent. Reduction of the "active" pentafluorophenyl ester **10** with $NaBD_4$ in dimethoxyethane gave alcohol **11** in 80% yield after flash chromatography. In order to assess the extent of regioselectivity, the effects of temperature and solvent were



investigated. Our results indicate that reaction temperature has little influence on the ratio of isomers. For example, a ~ 3% regioisomeric ratio difference was observed for MeOH over a range of 25-65°C.[10] The ratio, however, exhibited higher solvent dependence; for benzene, THF, 0.05-3M $LiClO_4$-THF, EtOAc, DCM, CH_3CN, DMSO, DMF the ratio varied from 82:18 to 91:9; for MeOH a 78:22 mixture of isomers was obtained. Several attempts to further improve the regiochemical outcome by varying the solvent and conditions for the reaction were to no avail.

In order to demonstrate the feasibility of library synthesis, several model compounds **7** (R_1= CH_2CONH_2; R_2,R_6= Me; R_3,R_4= Bzl; R_3-R_4= piperidyl; R_5= Bzl, ^{i}Pr) were synthesized on solid-phase and characterized after cleavage from the solid support.[11] All substituted cyclopentanes **7** were obtained in high yield (83-90%) and purity > 90%. One significant finding to emerge from our initial studies is that primary amines, when used in the first

Scheme 2



a) CD_3OD, NEt_3, CH_2Cl_2; b) pentafluorophenol, DCC, CH_2Cl_2; c) $NaBD_4$, DME.

two coupling steps (R_1NH_2 and R_3NH_2), cause the cyclic imide formation in following coupling steps, thus lowering the number of randomization steps. Therefore, to maximize library diversity, we recommend employing sets of secondary amines in the first two positions and primary and/or secondary amines in the third position (R_2NH_2).

Semiempirical calculations employing the AM1 Hamiltonian have also been carried out on the acetylated analogue of **6**, providing reasonable geometries of the transition structures for both reaction pathways (Figure 1).[12] The origin of observed regioselectivity is, however, unclear from the available data and one can only speculate that either stabilization of the developing negative charge by intramolecular hydrogen bonding (**TS-1**) or adverse steric interactions and charge repulsion (**TS-2**) are responsible for the observed selectivity. In support of the former hypothesis (**TS-1**) is the observed unfavorable effect of methanol on the regioisomeric ratio (*vide supra*). This would be expected from strongly solvated TS where hydrogen bonding coming from the bulk solvent competes effectively with the intramolecular amide N-H...O=C interaction. On the other hand, the dependence of regioselectivity upon the temperature suggests a higher $\Delta H^{\ddagger}$ and more favorable $\Delta S^{\ddagger}$ for **TS-2** which would be consistent with the latter hypothesis based on adverse stereoelectronic effects. In order to substantiate the involvement of the amide proton in **TS-1** and obtain further experimental evidence to support this hypothesis,

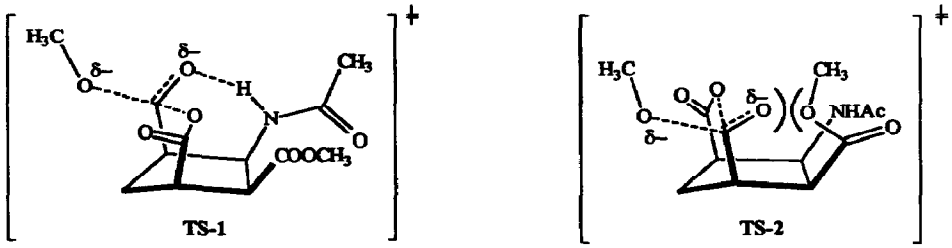


Figure 1: Transition structures for the reaction of methoxide anion with acetyl analogue of anhydride **6**.

kinetic solvent isotope effects and detailed proton inventory studies on model compounds have been initiated.

In summary, we have described the synthesis and preliminary investigations which suggest a considerable scope and adaptation of template **6** for the regioselective synthesis of libraries consisting of diverse, functionalized secondary and tertiary amides.

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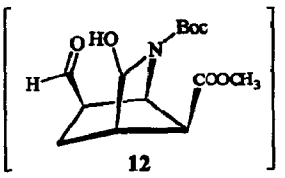
8. The intermediacy of Boc protected hemiaminal **12** would seem likely in this oxidation.



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9. In all experiments, ratios of **8A** : **8B** were determined by integration of appropriate resonances in the ^{1}H NMR spectrum recorded both in $CDCl_3$ and d_6-DMSO.
10. Expected effect of lowering the **8A**:**8B** ratio with an increase of the temperature was observed.
11. **General experimental procedure:** 1. Attachment of the scaffold **6** on sarcosyl-SCAL-TentaGel resin (DCM, NEt_3, 2h); 2. Coupling of secondary amine (10equiv) to the free carboxyl group (BOP, NEt_3, 8h); 3. Hydrolysis of methyl ester (0.5% NaOH, 1h) followed by coupling of primary/secondary amine (10equiv, BOP, NEt_3, 8h), 4. Boc group deprotection (TFA, 20min) followed by acetylation with Ac_2O, NEt_3 (10equiv, 5h). All compounds were characterized by ^{1}H-NMR and ES-MS spectra. For SCAL-anchoring, see ref. 13.
12. AM1 transition state calculations were performed with the MOPAC 5.0 package of programs adapted to Sybyl 6.00. Both TS's were characterized by exactly one negative force constant in their diagonalized Hessian matrix.
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