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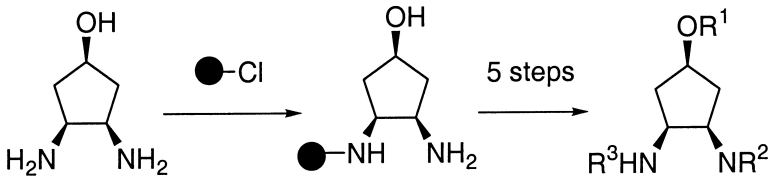

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Reports

Synthesis of Compound Libraries Based on 3,4-Diaminocyclopentanol Scaffolds

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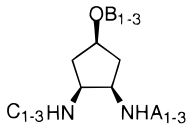
Combinatorial synthesis has recently emerged as a powerful tool for research in drug discovery.[1] A common strategy is to build libraries around a central core or scaffold.[2−9] The scaffold serves as a framework for the organization of substituents in space. Variation in the substituents provides the main source of diversity. In most reported cases, the core components have been relatively large (M_r >200). Given that the upper size limit for an effective drug molecule is generally considered to be $M_r \sim 500$, substituent size and diversity become severely limited.

We recently reported the synthesis of stereoisomeric diaminocyclopentanols **1** and **2**.[10] These and the related trans stereoisomers are of interest as scaffolds because they have a low molecular weight (116), well-defined, but variable stereochemistry (four possible 3,4-diaminocyclopentanol stereoisomers), and a relatively rigid core. We report here the synthesis of compound libraries based on core molecules **1** and **2**.

Considering the complications of characterization, the problems associated with biological assays of complex mixtures (for example, a mixture may contain both agonists and antagonists), and recent advances in high throughput parallel synthesis of individual compounds in 96-well and 384-well formats, we focused on the development of an effective strategy for parallel synthesis on solid support. The procedure for synthesizing a cyclopentane core with different pendant groups attached at each of the three nucleophilic sites involved six fundamental steps. The steps include the following: (1) linking the core molecule to a trityl resin,

Table 1. Library on Cores **1** and **2**



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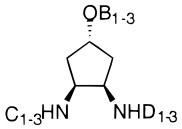

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core 1	yield %[a]	purity %	core 2	yield %[a]	purity %
A1B1C1	q	38	D1B1C1	44	82
A1B1C2	q	21	D1B1C2	47	86
A1B1C3	q	32	D1B1C3	87	82
A1B2C1	q	38	D1B2C1	52	23
A1B2C2	q	47	D1B2C2	54	39
A1B2C3	q	20	D1B2C3	59	25
A1B3C1	q	30	D1B3C1	49	50
A1B3C2	q	25	D1B3C2	45	50
A1B3C3	q	37	D1B3C3	69	30
A2B1C1	q	53	D2B1C1	q	20
A2B1C2	q	60	D2B1C2	q	47
A2B1C3	76	77	D2B1C3	q	27
A2B2C1	73	66	D2B2C1	q	50
A2B2C2	q	61	D2B2C2	q	61
A2B2C3	60	77	D2B2C3	q	52
A2B3C1	q	40	D2B3C1	q	63
A2B3C2	q	63	D2B3C2	q	32
A2B3C3	q	70	D2B3C3	q	62
A3B1C1	68	89	D3B1C1	q	61
A3B1C2	56	91	D3B1C2	q	70
A3B1C3	46	89	D3B1C3	70	62
A3B2C1	47	92	D3B2C1	q	64
A3B2C2	82	84	D3B2C2	q	73
A3B2C3	62	87	D3B2C3	q	81
A3B3C1	q	85	D3B3C1	q	65
A3B3C2	q	27	D3B3C2	82	80
A3B3C3	95	77	D3B3C3	q	74

[a] q indicates that the total weight of product was equal to or greater than the theoretical weight due to impurities.

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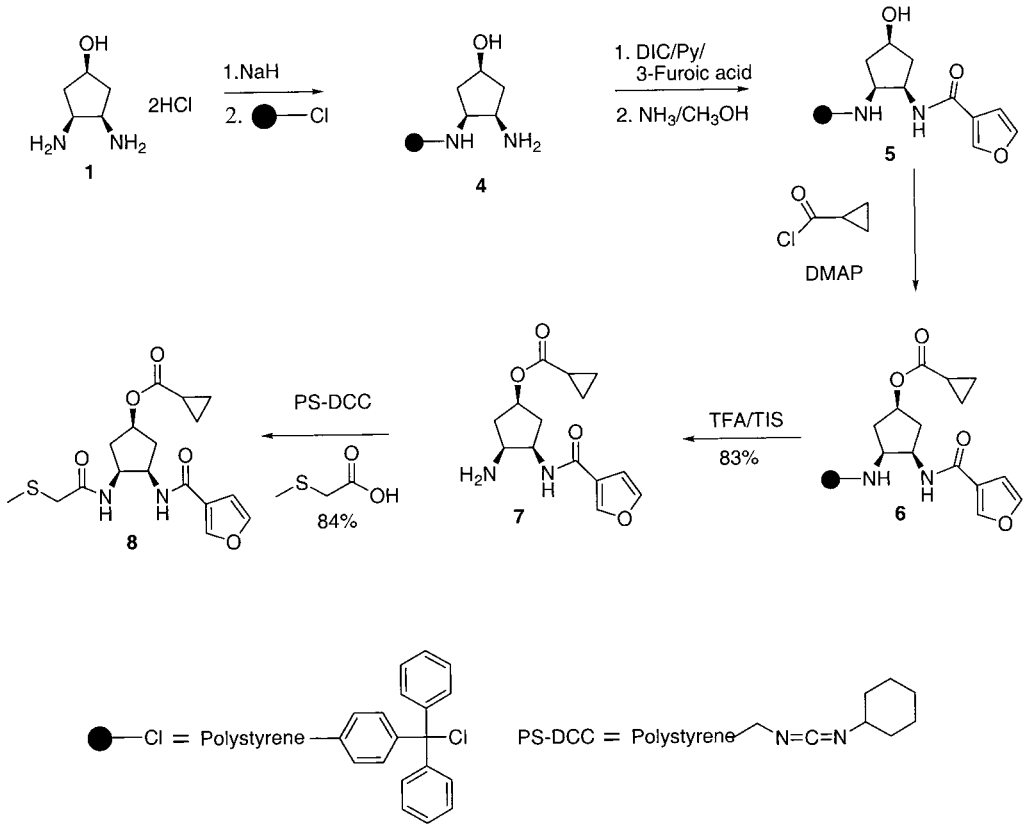
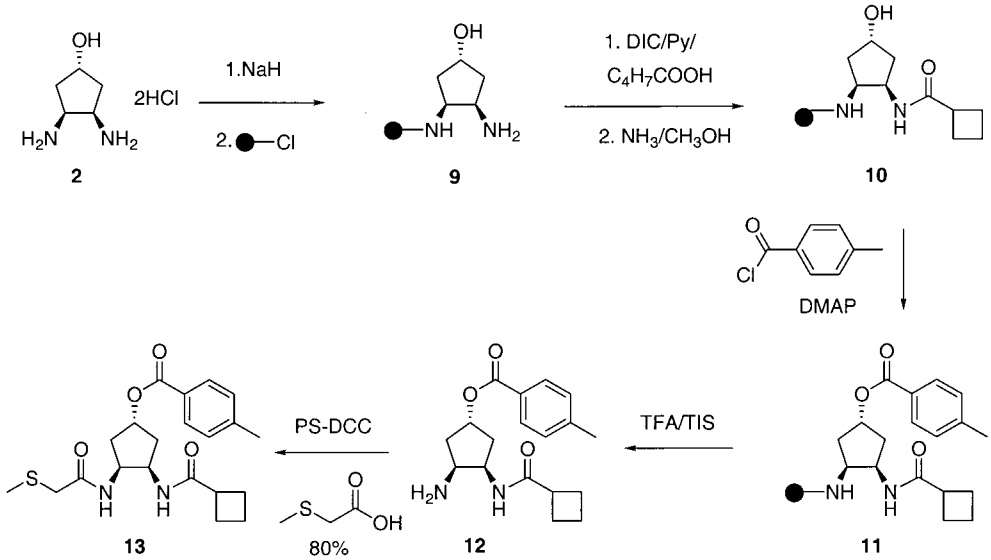
Scheme 1. Synthesis of a Trisubstituted 3,4-Diaminocyclopentanol on Core **1**



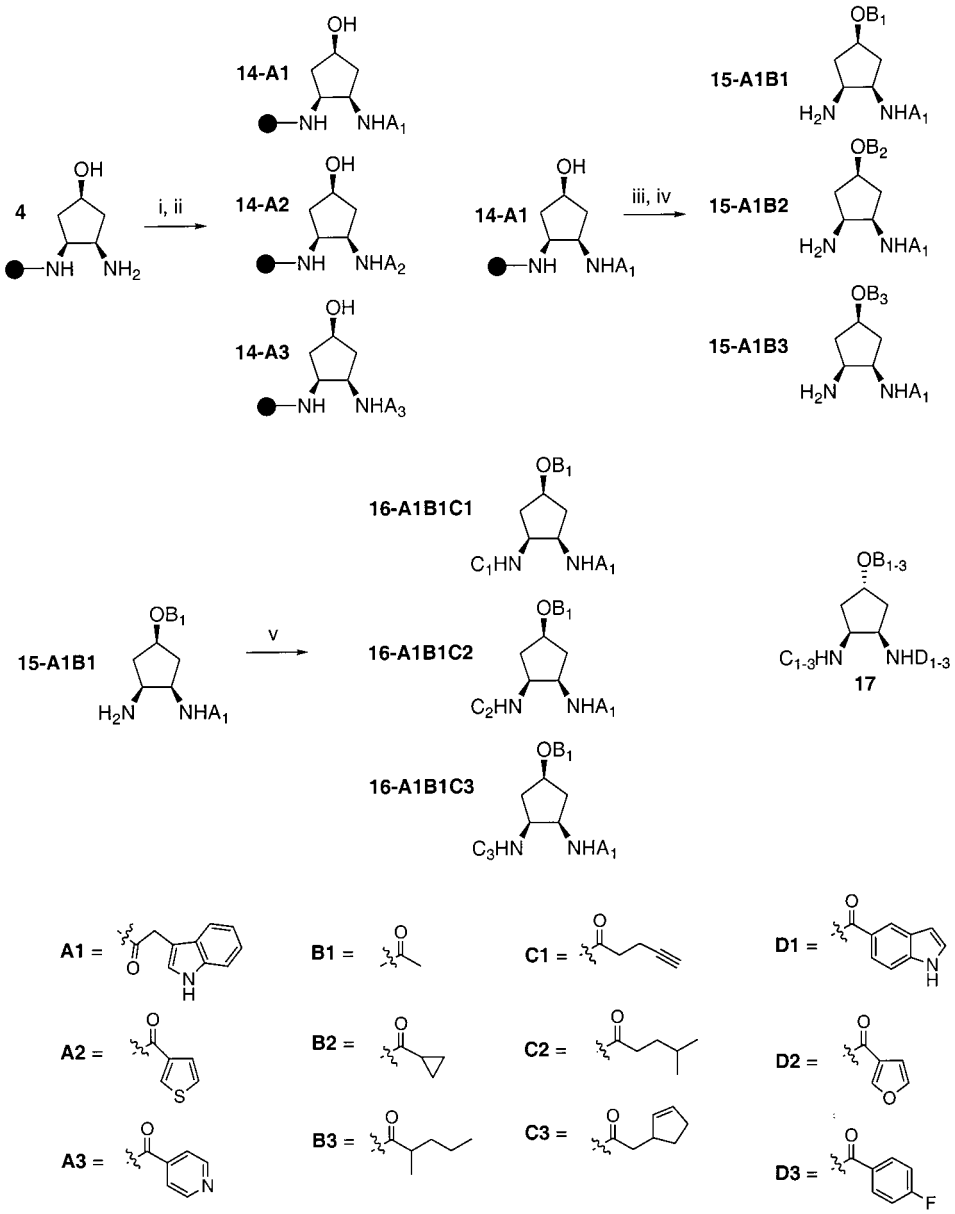
Scheme 2. Synthesis of a Trisubstituted 3,4-Diaminocyclopentanol on Core **2**



(2) coupling the first pendant group by reaction of the core-conjugated resin with an activated carboxylic acid, (3) ammonia treatment to cleave a transient ester, (4) coupling the second pendant group using a carboxylic acid chloride, (5) releasing the disubstituted diaminocyclopentanol from the support with trifluoroacetic acid, and (6) coupling the third pendant group using a solid-support carbodiimide activated carboxylic acid. Scheme 1 shows one example of this strategy. To develop the procedure, it was necessary to assess the outcome following each step. This was facilitated by using three pendant groups (2-furylcarbonyl, cyclopropylcarbonyl, and methylthioacetyl) which show significantly different chemical shifts in the proton NMR spectra, thereby allowing the reactions to be easily monitored by NMR.

Dihydrochloride salt **1** was treated with 2 equiv of sodium hydride and reacted with a trityl chloride resin (Nova-Biochem, loading range about 1 mmol/g) in *N*,*N*-dimethylformamide (DMF) to give the resin-bound amino alcohol **4**. Since reaction can occur with equal probability at either amino group, polymer **4** contains a racemic mixture of products. The resin-bound amino alcohol **4** was allowed to react with excess 3-furoic acid in the presence of 1,3-diisopropylcarbodiimide (DIC)/pyridine and then treated with ammonia in methanol to give the amido alcohol **5**. The

Scheme 3. Parallel Synthesis Strategy for Generation of Trisubstituted Cyclopentane Libraries[a]



[a] Reaction conditions: (i) acid/DIC/Py; (ii) NH_3/MeOH/40 °C; (iii) acid chloride/DMAP; (iv) TFA/TIS; (v) acid/PS-DCC.

purpose of the ammonia treatment was to cleave the ester that may have formed by reaction between the cyclopentane hydroxyl group and the activated carboxylic acid. The IR spectra of two compounds confirmed this transformation. There is a peak at 1725 cm^{-1} (typical carbonyl stretch for esters) that appeared following the coupling reaction, which disappeared after ammonia treatment. The resin was treated with cyclopropanecarbonyl chloride in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) to give resin-bound amido ester **6**. A dichloromethane (DCM) solution containing 4% trifluoroacetic acid (TFA) and 5% triisopropylsilane (TIS) was used to cleave amine **7** from the trityl resin. Amine **7** was isolated by evaporation of the DCM solution and used in the subsequent step without purification. 2-(Methylthio)-acetic acid was allowed to react with *N*-cyclohexylcarbodiimide-*N*′-methylpolystyrene to form an activated intermediate, which underwent nucleophilic attack by amine **7** to give product **8** in 83% yield. HPLC analysis using a PRP-1 column eluting with water and acetonitrile (gradient, detection by UV at 254 nm) allowed estimation of the product purity. Assuming that the impurities have similar extinction coefficients, the unpurified product contained 77% compound **8** and 23% side products and impurities, which were not identified.

The use of core **2** as scaffold to construct a trisubstituted cyclopentane is illustrated in Scheme 2. Resin-bound **9** was reacted with cyclobutane carboxylic acid in the presence of DIC followed by ammonia treatment to give amido alcohol **10**. The latter was treated with *p*-toluoyl chloride and DMAP to afford intermediate **11**, which was cleaved by TFA/TIS solution to give amine **12** in 83% yield. Activated 2-(methylthio)acetic acid was reacted with **12** to generate trisubstituted cyclopentane **13** in 80% yield. The reaction products from each step were characterized by ^1H NMR and MS (Supporting Information).

To more completely test the utility of the synthetic

strategy, we selected a group of carboxylic acids (indole-3-acetic acid, 3-thiophenecarboxylic acid, and isonicotinic acid) which were allowed to react with **4** to yield three resin-support monosubstituted compounds: **14-A1**, **14-A2**, and **14-A3** (Scheme 3). Because of variations in solubility of carboxylic acids, we determined that it was possible to do the coupling reactions in either dichloromethane (DCM) or DMF. Each compound−resin conjugate was split into three equal portions and allowed to react with three different acid chlorides (acetyl chloride, cyclopropanecarbonyl chloride, and 2-methylpentanoyl chloride) to afford nine resin-supported disubstituted compounds (**15-A1B1**, ..., **15-A3B3**). TFA and TIS solution cleaved the compounds from the trityl resin, and each of the nine resulting compounds was split into three equal portions and allowed to react with one of three activated acids (4-pentynoic acid, 4-methylpentanoic acid, and 2-cyclopentene-1-acetic acid). In this way, 27 trisubstituted compounds (**16-A1B1C1**, ..., **16-A3B3C3**) were generated as illustrated in Scheme 3. By the same method, core molecule **2,** which is an epimer of **1**, was also used to construct 27 trisubstituted compounds, **17**. However, three acids, **D1**−**3**, were used in place of **A1**−**3**. The purity was determined by HPLC, and yields were calculated based on the weight of each compound (Table 1).

In summary, we have developed a strategy for parallel synthesis of a unique set of compounds based on the diaminocyclopentanol scaffolds. Compound **8** and **13**, which are representative of the structures that can be obtained by this strategy, have low molecular weight (366 and 404, respectively) and variable stereo structures. The availability of a wide variety of carboxylic acids such as aliphatic, aromatic, and amino acids, as well as other electrophiles that can be linked to the amino or hydroxyl sites, and the stereochemical variation available within the trisubstituted cyclopentane framework open the door to the synthesis of large, highly diverse, small molecule (M_r <500) libraries around these scaffolds.

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Supporting Information Available. Experimental procedures to synthesize compounds **8** and **13** and libraries **16** and **17**; ^{1}H NMR spectra for compounds **7**, **8**, **12**, and **13**; IR spectra of **8**; an IR comparison before and after ammonia treatment of a resin-bound ester; MS for **7**, **8**, **13**, **16-A1B1C3**, and **17-D3B2C3**; and HPLC chromatograms of **8**, **16-A1B1C3**, and **17-D3B2C3**. This information is available free of charge via the Internet at http://pubs.acs.org.

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