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Combinatorial Libraries Based on a Novel and Readily Accessible "Centroid" Scaffold

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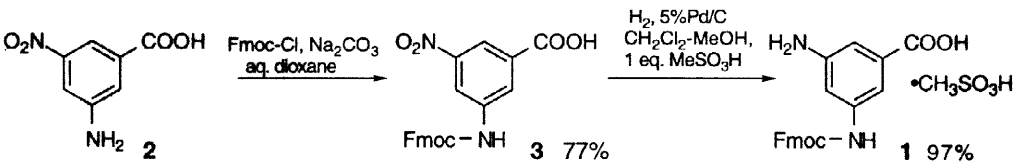
Dedicated to the memory of our esteemed consultant Sir Derek H.R. Barton

Abstract: A convenient large-scale preparation of the trifunctional acid **1** has been developed. This acid serves as a useful scaffold for construction of combinatorial libraries incorporating three variable elements in a centro-symmetric array.

Combinatorial libraries have proven a highly useful tool in the drug discovery process.[1] Many libraries have been constructed around novel core moieties which allow varied presentation of sets of potential binding groups.[2] We were especially interested in a practical "centroid" core which would allow presentation of three independent sets of building blocks in a centro-symmetric fashion. To avoid possible interaction between the three functional groups on the core, we selected a 1,3,5-trisubstituted benzene core as embodied in **1**. This Letter discusses facile preparation and use of this moiety for construction of combinatorial libraries.

Acid **2** is commercially available,[3] and convenient large-scale preparation has been described.[4] We have converted **2** to Fmoc-derivative **3** under typical Fmoc conditions. This material may be recrystallized. Hydrogenation of **3** with Pearlman catalyst gave a 56% yield of **1** as the free base, together with 40% 9-methylfluorene resulting from cleavage and reduction of the Fmoc group. Free amine **1** is not stable on long standing. To eliminate these problems, we reduced **3** with Pd/C in the presence of $MeSO_3H$, providing the salt **1** in high yield and purity.[5] This salt is stable on storage.



We initially anticipated that orthogonal protection of the two amino groups in **1** would be required for its use in solid-phase synthesis. We have found, however, that such protection is unnecessary, and **1** can be employed directly for preparation of high-purity combinatorial libraries.

To examine the use of **1** in solid-phase synthesis, we prepared functionalized resin **4**. This incorporates SASRIN[6] resin for facile release of ligand with dilute TFA, a C-terminal Trp moiety to ensure ready UV detection of all cleaved ligands, and an N-terminal Ile moiety as a challenging nucleophile (hindered, not strongly basic). Attachment of **1** to resin **4** with HBTU/HOBt[7] efficiently provided **5**, as evidenced by clean product **6** (see Figure 1[8]) obtained after cleavage from the resin with CH_2Cl_2-TFA-H_2O 99:1:0.05. The absence of other products attests to the low reactivity of the aromatic amino-group, since 3 equivalents of **1** were employed in the acylation reaction. For further acylation of **5**, we selected Boc-valine as a challenging acylating agent. While this acylation could not be achieved under typical carbodiimide

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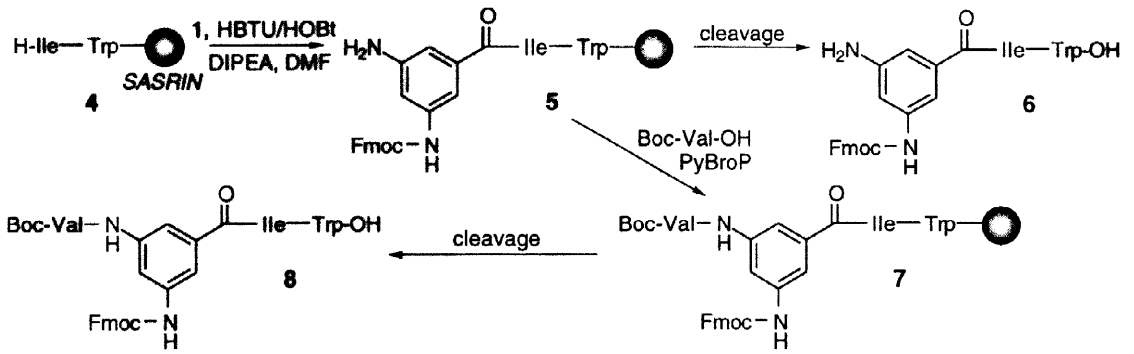
conditions, clean conversion to the amide **6** was accomplished with the more reactive agent **PyBroP**.[9] Cleavage from the resin furnished cleanly product **8** (see Figure 2).



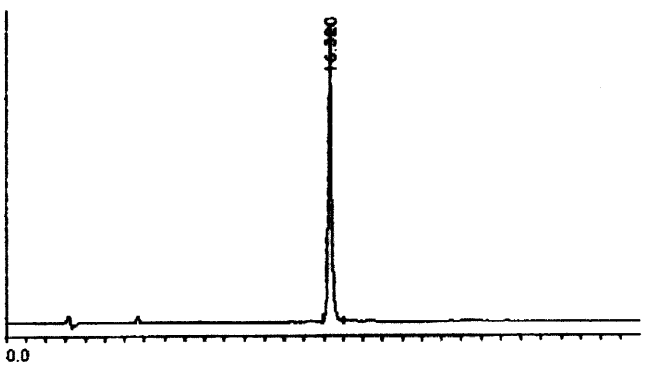


Figure 1. Crude compound **6**.

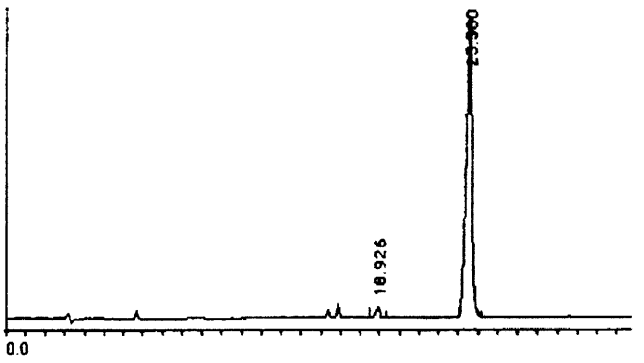
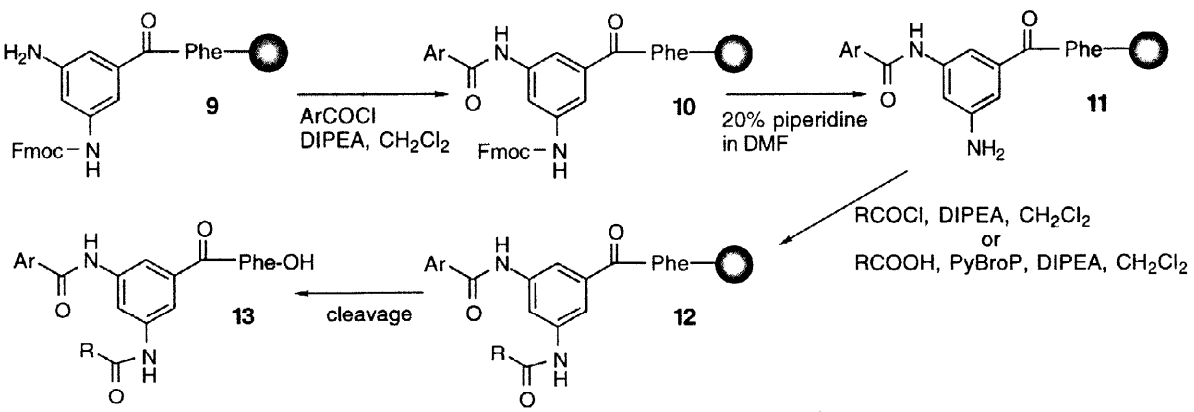
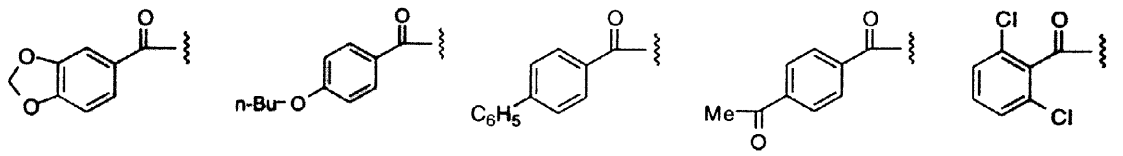


Figure 2. Crude compound **8.**

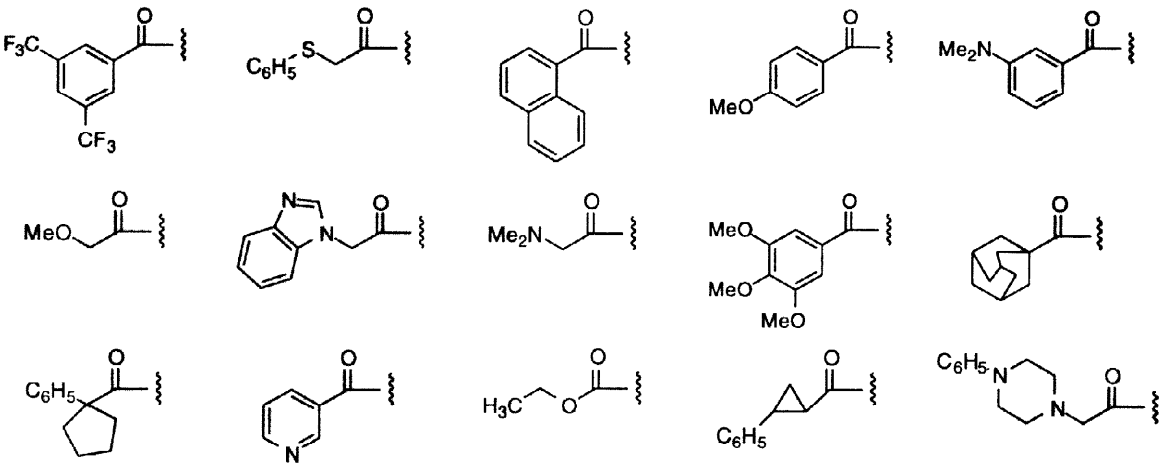
For preparation of a triply-variable library, we elected to use 2-chlorotrityl resin instead of SASRIN resin, since yields ranged from 80-90% with the former and 40-60% with the latter, based on stated capacity of the resin. We attached **1** to different aminoacyl chlorotrityl resins[10] to give elaborated resins, one example of which is Phe-resin **9**. We then acylated the resin with an acid chloride. In our initial set, we employed five aroyl chlorides, with either electron-donating or electron-withdrawing substituents, as well as a 2,6-disubstituted example. All reactions proceeded cleanly to products **10**. The Fmoc group was then removed with piperidine/DMF to give amines **11**. These amines were then acylated with a broader range of acyl chlorides (a portion of set shown) to furnish the fully acylated materials **12**. Cleavage from the resin then afforded library compounds **13**.[11] HPLC purity was generally >97%. When the carboxylic acid, but not the acid chloride was available, PyBroP coupling[12] (two cycles) was conducted. Purity was generally >95%, always >90%.



ArCO-



RCO-



In certain trial examples where the aroyl group in **11** was strongly deactivating, such as 3,5-bis(trifluoromethyl)benzoyl, product purity was not high. In these cases, unacylated amine was present, since the second acylation to **12** was difficult to force to completion. This problem was resolved by introduction of the non-deactivating acyl group first, then deactivating aroyl group. This sequence ensured complete reaction in the acylation steps.

As aminoacyl components for these "centroid" libraries we have employed all of the natural aminoacids, with reactive side-chains protected in TFA-labile form. A set of non-natural aminoacids has also been demonstrated. The products are not limited to carboxylic acids, since we have demonstrated the removal of the C-terminal acid from the resin in the form of an amide[13] or ester.[14] In conjunction with several non-acid modes of attachment to resin, very broad libraries are accessible by this methodology.

In summary, the "centroid" core unit **1** was prepared readily on large scale. By sequential attachments at the three functional groups, extensive triple-variable combinatorial libraries were constructed efficiently and in high purity.

References and Notes

1. Recent reviews on combinatorial chemistry and applications in drug discovery:
   (a) Bristol, J.A., Ed. *Tetrahedron*, **1997**, *53*, 6573.
   (b) Szostak, J., Ed. *Chemical Reviews*, **1997**, *97*, 347.
   (c) Beutel, B.A. *Ann. Reports Med. Chem.* **1997**, *32*, 261.
   (d) Plunkett, M.J.; Ellman, J.A. *Scientific American* **1997**, *276(4)*, 68.
   (e) Hogan, J.C. *Nature Biotech.*, **1997**, *15*, 328.
2. A centro-symmetric library based on Kemp's triacid: Kocis, P.; Issakova, O.; Sepetov, N.; Lebl, M. *Tetrahedron Lett.* **1995**, *36*, 6623.
   A centro-symmetric library based on 3-amino-5-hydroxybenzoic acid: Dankwardt, S. M.; Phan, T. M.; Krstenansky, J. L. *Mol. Diversity* **1996**, *1*, 113.
   A centro-symmetric library based on triaminotriazine: Stankova, M.; Lebl, M. *Mol. Diversity* **1996**, *2*, 75.
3. Lancaster Synthesis, catalog no. 6046. Also available from other suppliers.

4. (a) Terpko, M.O.; Heck, R.F. *J. Org. Chem.* **1980**, *45*, 4992.
(b) Georg, G.I.; Boge, T.C.; Park, H.; Himes, R. H. *Bioorg. Med. Chem. Lett.* **1995**, *57*, 615.

5. Preparation of **1**: To an N_2-degassed solution of Na_2CO_3 (14.6 g, 138mmol) in water (160 mL) was added nitro-acid **2** (10.0 g, 55mmol) in dioxane (130 mL). The mixture was cooled to 5°C, and Fmoc-chloride (14.2 g, 55mmol) in dioxane (90 mL) was added dropwise over 15min. The mixture was stirred in the bath 30min., then 24h. without the bath. The solid was filtered and washed with water (40 mL). The filtrate was concentrated to 160 g, allowed to cool, filtered and washed with water. The two solids were combined, stirred with water (75 mL) for 30min., filtered and washed. The procedure was repeated with ether (100 mL), then the solid partitioned between 250 mL each EtOAc and 1N HCl. The EtOAc was washed with brine, dried over $MgSO_4$ and concentrated. Drying at 0.1mm left 18.9 g of **3** as a yellow solid, m.p. 249-52°C, single component HPLC.
In a one-liter Parr bottle were placed 5% Pd/C (1.5 g), CH_2Cl_2 (225 mL), MeOH (175 mL), Fmoc-acid **3** (15.5 g, 38mmol), and $MeSO_3H$ (3.6 g, 38mmol). The mixture was hydrogenated at 50 psi for 40 min, then filtered. The filtrate was concentrated and the residue treated with EtOAc (100 mL) and MeOH (4 mL). Filtration and drying left 8.7 g powder. The initial catalyst-containing solid was treated withMeOH (300 mL) and CH_2Cl_2 (50 mL). Concentration left a solid which was treated with EtOAc-MeOH as above to provide 9.4 g solid. The two solids **1** were combined. The product shows clean PMR, with 0.7 equiv. MeOH, and HPLC gives a single peak.

6. A dialkoxybenzyl alcohol resin obtained from BACHEM: Mergler, M.; Tanner, R.; Gosteli, J.; Grogg, P. *Tetrahedron Lett.* **1988**, *29*, 4005.

7. Knorr, R.; Trzeciak, A.; Bannwarth, W.; Gillessen, D. *Tetrahedron Lett.* **1989**, *30*, 1927.

8. Vydac column, 25-95% MeCN-H_2O gradient (0.1%TFA), 1ml/min., UV detection at 254nM.

9. PyBroP=bromo-tris-pyrrolidinophosphonium hexafluorophosphate: Coste, J.; Frerot, E.; Jouin, P.; Castro, B. *Tetrahedron Lett.* **1991**, *32*, 1967.

10. Obtained from AnaSpec Inc., San Jose, CA.

11. Utilization of **1** in library synthesis: Aminoacyl resin (0.30g, 0.15mmol)) was treated with salt **1** (3 equiv.), 0.5M HBTU/HOBt in DMF (3 equiv.) and DIPEA (12 equiv.) for 1.5 h., followed by DMF and CH_2Cl_2 washes, 5x20ml each.. All agitation was achieved by nitrogen sparge through a fritted plate. Resin (0.10g) was then treated with aroyl chloride (10 equiv.) and DIPEA (20 equiv.) in CH_2Cl_2 for 1.5 h, followed by DMF and CH_2Cl_2 washes, 3x10ml each. The Fmoc group was removed by two 15 min. treatments with 20% piperidine/DMF. The second acylation with acyl chloride was conducted under the same conditions as the first. If this reaction was not complete (HPLC), the procedure was repeated.
For cleavage, the resin was treated with CH_2Cl_2-TFA-H_2O 99:1:0.05 (three 15min. cycles) and the combined filtrates concentrated in vacuo.

12. PyBroP (10 equiv.), RCOOH (10 equiv.), DIPEA (20 equiv.), CH_2Cl_2, 18h. shaking.

13. Yang, L.; Guo, L. *Tetrahedron Lett.* **1996**, *37*, 5041.

14. Ester formation by cleavage from the resin with alkoxide or with methanol+amine have been utilized:
(a) Fagnola, M.C.; Candiani, I.; Visentin, G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2307
(b) Cheng, Y.; Chapman, K.T. *Tetrahedron Lett.* **1997**, *38*, 1497.
As an alternative, we have conducted successful cleavage with HCl/MeOH to yield methyl esters.