Polymer Bound 3-Hydroxy-2-methylidenepropionic Acids. A Template for Multiple Core Structure Libraries

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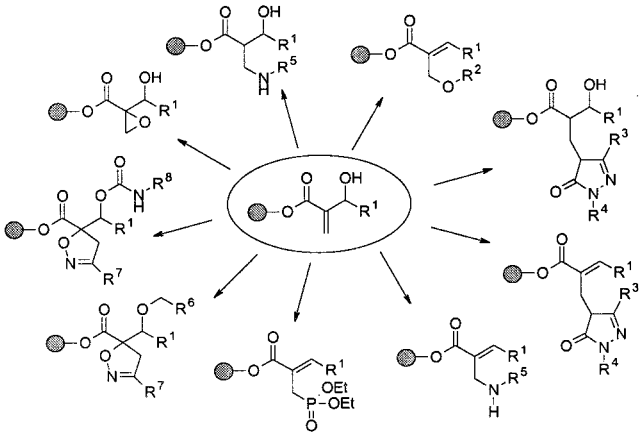
Combinatorial chemistry[1] has become an important tool for the synthesis of small organic molecules which may serve as new lead structures in the drug discovery process. Many of these libraries are based on the solid phase synthesis of a single core structure bearing different substituents. However, for random screening it is important to have structurally different cores containing different commercially available building blocks. Therefore, the synthesis of flexible templates is very promising, since not only the substituents of one core molecule can be varied, but also the type of core derived from this template.

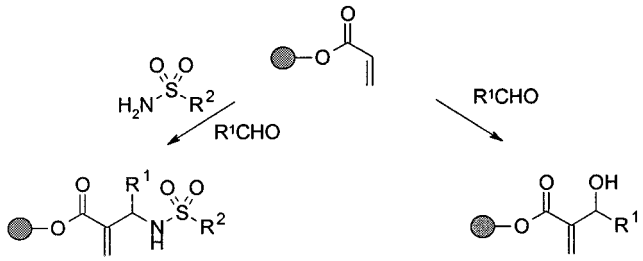
Tempest and Armstrong[2] have successfully shown the use of squaric acid as a template for multiple core structure libraries (MCSL). Here we present polymer bound 3-hydroxy-2-methylidenepropionic acid as an excellent template for the synthesis of MCSL's. In only a few steps a significant number of different linear and heterocyclic cores can be constructed (Scheme 1).

Scheme 1



Polymer bound acrylic ester is reacted in a Baylis−Hillman reaction[3] with aldehydes to form 3-hydroxy-2-methylidenepropionic acids[4] or with aldehydes and sulfonamides in a three-component reaction to form 2-methylidene-3-[(arylsulfonyl)amino]propionic acids[5] (Scheme 2).

Scheme 2

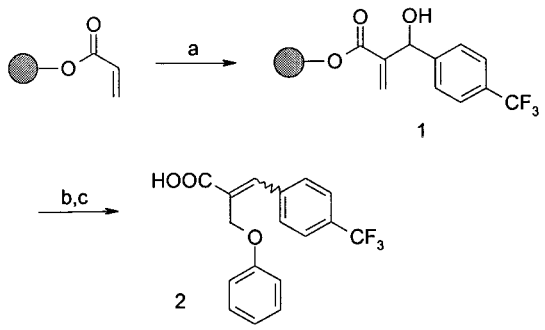


Though both structures can be used as templates for the synthesis of MCSL's, in this paper we demonstrate the application of the resin bound 3-hydroxy-2-methylidenepropionic acids. Due to the presence of two functional groups, there is a wide range of possible postmodifications. One possibility is the conversion of the double bond, as in the Michael addition of amines leading to 1,3-amino alcohols,[4] by epoxidation or a Michael addtion of a β-keto ester to form pyrazolones after the conversion into the hydrazones followed by an intramolecular cyclization.

Another possibility is to carry out further reactions involving the hydroxy function, for example in a Mitsunobu reaction, whereby the double bond is rearranged in a manner similar to the synthesis of allylic amines.

The final option is to convert both functional groups in one reaction step. During the synthesis of isoxazolines[6] via a 1,3-dipolar cycloaddition with nitrile oxides,[7] the hydroxy function reacts with phenyl isocyanate which is used to dehydrate the nitroalkane to form a carbamate.

Scheme 3[a]



[a] Key: (a) 16 equiv of 4-trifluoromethylbenzaldehyde, 10 equiv of DABCO, $CHCl_3$/DMSO 1:1 rt, 2 d, double coupling; (b) 6 equiv of phenol, 3 equiv of DIAD (diisopropyl diazodicarboxylate), 3 equiv of PPh_3, THF, rt, 3 h; (c) 5% TFA/CH_2Cl_2, rt, 30 min.

The starting point for all of these reactions is the Baylis−Hillman reaction itself. For this reaction we chose 4-(trifluoromethyl)benzaldehyde (Scheme 3) and the re-

(1) Früchtel, J. S., Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17−42. Hermkens, P. H. H., Ottenheijm, H. C. J., Rees, D. *Tetrahedron* **1997**, *53*, 5643−5678. Brown, R. *Contemp. Org. Synth.* **1997**, 216−237.

(2) Tempest, P. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7607−7608.

(3) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001−8062.

(4) Richter, H.; Jung, G. *Mol. Div.* **1998**, *3*, 191−194. See also: Prien, O. Rölfing, K.; Thiel, A., Künzer, H. *Synlett* **1997**, 325−326.

(5) Richter, H.; Jung, G. *Tetrahedron Lett.* **1998**, *39*, 2729−2730.

(6) Richter, H.; Höltzel, A.; Jung, G. In *Innovation and Perspectives in Solid-Phase Synthesis and Combinatorial Libraries*; Epton, R., Ed.; Mayflower Scientific Limited: Birmingham, in press.

(7) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339−5340.

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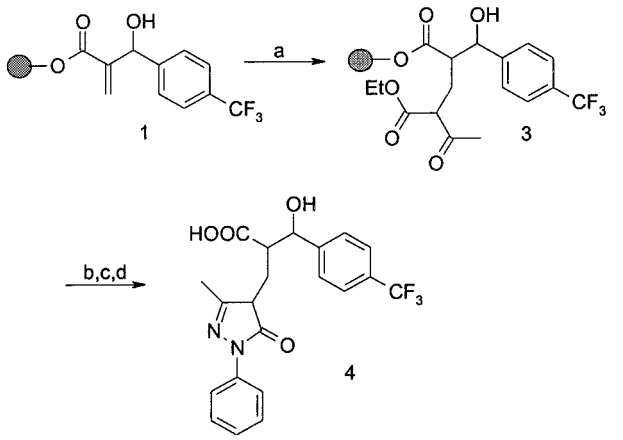
Scheme 4[a]



[a] Key: (a) 5 equiv of ethyl acetoacetate, 2 equiv of BEMP, THF, rt, 4 h; (b) 10 equiv of phenylhydrazine hydrochloride, 10 equiv of DIEA, 20 equiv of TMOF, THF, rt, 8 h; (c) 5% TFA/CH_2Cl_2, rt, 30 min.

sulting polymer bound allylic alcohol **1** in order to establish the synthesis of the different cores.

First we carried out the Mitsunobu reaction[8] with phenol under standard reaction conditions (Scheme 3). This reaction proceeded very well, and we obtained only the S_N'-reaction product **2**.[9]

The incorporation of diverse aromatic and heteroaromatic aldehydes and diverse substituted phenols gave excellent purities (65−98%) as determined by analytical HPLC (λ = 214 nm).

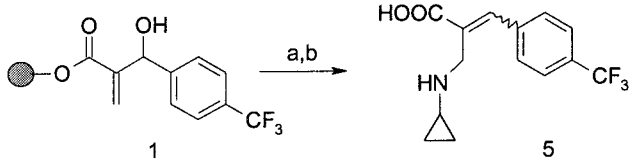
To show the possibility of Michael additions, we chose the synthesis of pyrazolones[10] (Scheme 4). The Michael addition was carried out with ethyl acetoacetate and BEMP[11] as base to form the resin bound β-keto ester **3**. This was then transformed into the hydrazone with phenylhydrazine hydrochloride in the presence of TMOF and DIEA. During cleavage with 5% TFA in CH_2Cl_2 the hydrazone cyclized to form the pyrazolone **4** with a purity of 81% (analytical HPLC) and an isolated yield of 80%.

Following this procedure 30 different pyrazolones were synthesized in good purities (44−85%).

To allow for a diverse multistep synthesis we transformed the 3-hydroxy-2-methylidenepropionic acid **1** (Scheme 5) into the polymer bound allylic amine **5**, an unusual β-amino acid. The polymer bound allylic alcohol **1** was first treated with acetyl chloride and DIEA in CH_2Cl_2 to form the ester, which was reacted with cyclopropylamine in an addition elimination step to form the allylic amine **5**.[12] After cleavage from the resin, **5** was obtained in good purity (87%) and yield (76%).

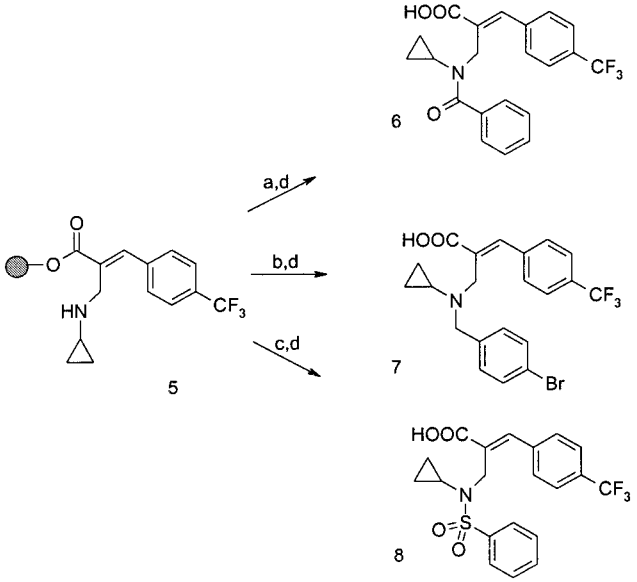
The polymer bound allylic amines **5** can be employed

Scheme 5[a]



[a] Key: (a) 10 equiv of acetic chloride, 10 equiv of DIEA, CH_2Cl_2, rt, 16 h; (b) 10 equiv of cyclopropylamine, 2 equiv of BEMP, DMF, rt, 6 h.

Scheme 6[a]



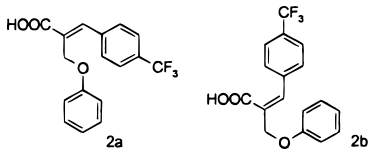
[a] Key: (a) 5 equiv of benzoic acid, 5 equiv of PyBroP, 10 equiv of DIAE, CH_2Cl_2/DMF, 1:1, rt, 4 h, double coupling; (b) 10 equiv of 4-bromobenzyl bromide, 4 equiv of BEMP, DMF, rt, 16 h; (c) 10 equiv of benzenesulfonylchloride, 10 equiv of DIEA, CH_2Cl_2 rt, 5 h; (d) 5% TFA/CH_2Cl_2, 30 min.

in several reactions. Scheme 6 shows acylation, alkylation, and sulfonation as possible modifications. For the acylation we used benzoic acid which was coupled for 3 h by using PyBroP[13] and DIEA in CH_2Cl_2/DMF 1:1. To drive the reaction to completion, a double coupling was necessary, and after cleavage we obtained the product **6** in high purity (89%) and yield (75%). Alkylation was performed with 4-bromobenzyl bromide and BEMP in DMF for 16 h. In this way we obtained the product **7** in high purity (87%) and yield (80%). The sulfonation was optimized with benzenesulfonyl chloride. The reaction was carried out with DIEA in CH_2Cl_2 for 5 h. After cleavage from the resin product **8** was obtained in high purity (84%) and yield (70%).

To investigate the use of different building blocks we applied 10 different examples of each building block and found good to excellent purities (60−92%) in the analytical HPLC (λ = 214 nm).

(8) Mitsunobu, O. *Synthesis* **1981**, 1−28.

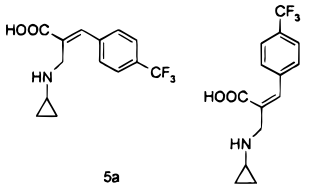
(9) NMR analysis using NOE difference spectroscopy shows that only **2a** was formed.



(10) Tietze, L. F.; Steinmetz, A. *Synlett* **1996**, 667−668.

(11) 2-(*tert*-Butylimino)-2-(diethylamino)-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine: Schwesinger, R.; Schlemper, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1212−1214.

(12) NMR analysis using NOE difference spectroscopy shows that only **5a** was formed.



(13) Bromotris(pyrrolidino)phosphonium hexafluorophosphate.

In summary we have shown the use of 3-hydroxy-2-methylidenepropionic acid as a template for the synthesis of multiple core structure libraries. In this case many reactions are carried out, e.g. the Mitsunobu reaction, the synthesis of pyrazolones, and the synthesis of allylic amines, which can be acylated, alkylated, and sulfonated. These reactions are only a small selection of the possiblities with this molecule and show the advantages of flexible templates.

Experimental Section

Reagents were purchased from Aldrich, Merck, Fluka, Bachem, and Novabiochem. 2-Chlorotrityl chloride resin (1,3 mmol/g, 1% DVB, 200−400 mesh) was purchased from Senn Chemicals. All yields reported are based on the initial loading of the resin.

^{1}H NMR and ^{13}C NMR spectra were recorded at a proton frequency of 250 MHz. NOE difference experiments were carried out at a proton frequency of 600.13 MHz. All samples were dissolved in 500 μL of DMSO-d_6.

Analytical HPLC was performed on a Waters instrument using a Grom NucleoSil C_{18} column (18 cm, 5 μm C_{18}, 0.3 mL/min, gradient from 90% aqueous media (0.1% TFA) to 100% CH_3CN (0.1% TFA)) with UV detection at 214 nm. High-resolution spectra were acquired on a Fourier-transform-ion-cyclotron-resonance (FT-ICR) mass spectrometer. The negative ions are generated with an external electrospray source (ESI). The LC-MS studies were performed with a ESI-mass spectrometer coupled with an ABI 140 solvent delivery system. For UV-detection a linear UVIS 204 photometer was used at 214 nm.

3-Hydroxy-2-methylidene-3-[4-(trifluoromethyl)phenyl]-propionic Acid (1). 2-Chlorotrityl chloride PS resin (40 mg, capacity: 1.3 mmol/g) was loaded with 4 equiv of acrylic acid (14.3 μL) in 600 μL of DMF/DCM (1:1) by using 6 equiv of Et_3N (43.5 μL) for 4 h at 0 °C. After washing, the resin was suspended in 300 μL of DMSO/$CHCl_3$ (1:1) and 16 equiv of 4-(trifluoromethyl)benzaldehyde (111.2 μL) and 10 equiv of DABCO (58 mg) were added and shaken for 2 d at room temperature. This step was repeated once. The resulting mixture was filtered and washed with DMF, EtOH, CH_2Cl_2, and Et_2O. **1** was cleaved with 600 μL of DCM/TFA (95:5) for 45 min and concentrated to dryness. After lyophilization from *tert*-BuOH/H_2O (4:1), we obtained a crude product with a purity of 97% in analytical HPLC. **1** was analyzed by MS and purified by preparative HPLC to obtain 10,9 mg (85% yield): ^{1}H NMR: δ = 5.50 (s, 1), 5.99 (s, 1), 6.21 (s, 1), 7.51 (d, 2, ^3J = 8.24 Hz), 7.67 (d, 2,^{3} J = 8.24 Hz); ^{13}C NMR: δ = 70.1, 123.8, 124.3 ($^1J_{CF}$ = 271 Hz), 124.8, 127.6, 127.6, 144.0, 148.0, 166.8; HRMS (ESI): [M − H]$^-$ calcd for $C_{11}H_8O_3F_3$: 245.043097, found: 245.043626.

2-(Phenoxymethyl)-3-[4-(trifluoromethyl)phenyl]acrylic Acid (2). Resin **1** (40 mg) reacted with 6 equiv of phenol (29.4 mg), 3 equiv of PPh_3 (40.9 mg), and 3 equiv of DIAD (30.1 μL) in a Mitsunobu reaction to form **2**. The reaction was carried out in THF for 3 h. The resin with the phenol and PPh_3 was cooled to 0 °C. The DIAD was added, and after 10 min at 0 °C the resin was shaken for 3 h at room temperature. The mixture was filtered and washed with DMF, EtOH, CH_2Cl_2, and Et_2O. **2** was cleaved with 600 μL of CH_2Cl_2/TFA (95:5) for 45 min and concentrated to dryness. After lyophilization from *tert*-BuOH/H_2O (4:1), we obtained a crude product with a purity of 98% in analytical HPLC. This was analyzed by MS and purified by preparative HPLC to obtain 14.9 mg (89% yield): ^{1}H NMR: δ = 4.74 (s, 2), 6.94 (m, 1), 6.98 (d, 2, J = 7.93 Hz), 7.70 (d, 2, J = 8.24 Hz), 7.79 (d, 2, J = 8.24 Hz), 8.00 (s, 1); ^{13}C NMR: δ = 62.4, 114.7, 115.7, 121.0, 124.3 ($^1J_{CF}$ = 271 Hz), 125.5, 129.5, 130.1, 130.2, 138.4, 142.1, 158.1, 167.7; HRMS (ESI): [M − H]$^-$ calcd for $C_{17}H_{12}O_3F_3$: 321.074396, found: 321.085600.

2-Acetyl-4-[[hydroxy-4-(trifluoromethyl)phenyl]methyl]-pentanedioic Acid 5-Ethyl Ester (3). Resin **1** (40 mg) was suspended in 700 μL of THF. Then 5 equiv of ethyl acetoacetate (33 μL) and 2 equiv of BEMP (30.1 μL) were added and shaken for 5 h at room temperature. After the resin was washed, **3** was cleaved with 600 μL of DCM/TFA (95:5) for 45 min and concentrated to dryness. After lyophilization from *tert*-BuOH/H_2O (4:1), the crude product had a purity of 80% (summary of all diastereomers) in analytical HPLC. The identity of **3** was confirmed by MS and HPLC-MS, and **3** was purified by preparative HPLC to obtain 14.2 mg (75% yield): ^{1}H NMR of one diastereomer: δ = 1.21 (t, 3, J = 7.0 Hz), 2.24 (s, 1), 2.99 (m, 1), 4.1 (m, 2), 5.17 (d, 1, J = 8.24 Hz), 7.60 (d, 2, J = 8.24 Hz), 7.77 (d, 2, J = 8.24 Hz); ^{13}C NMR of one diastereomer: δ = 14.2, 19.5, 24.5, 43.3, 59.5, 77.5, 100.4, 124.3 ($^1J_{CF}$ = 271 Hz), 125.3, 127.9, 143.1, 163.1, 166.7, 172.93; HRMS (ESI): [M − H]$^-$ calcd for $C_{17}H_{18}O_6F_3$: 375.106086, found: 375.127149.

3-Hydroxy-2-[(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)methyl]-3-[4-(trifluoromethyl)phenyl]propionic Acid (4). To resin **3** (40 mg) were added 10 equiv of phenylhydrazine hydrochloride (75.2 mg), 10 equiv of DIEA (89 μL), and 20 equiv of TMOF (113.9 μL) and suspended in 700 μL of THF. After the mixture was shaken for 16 h at room temperature, it was filtered and washed with DMF, EtOH, CH_2Cl_2, and Et_2O. During cleavage from the resin with 600 μL of CH_2Cl_2/TFA (95:5), **4** was formed by acid-catalyzed intramolecular cyclization within 30 min. After lyophilization from *tert*-BuOH/H_2O, we obtained a crude product with a purity of 81% (summary of all diastereomers) in analytical HPLC (λ = 214 nm). **4** was analyzed by MS and purified by preparative HPLC to obtain 17.5 mg (80% yield): ^{1}H NMR of one diastereomer: δ = 1.97/2.04 (m, 2), 2.04 (s, 3), 2.92 (m, 1), 4.73 (d, 1, J = 8.4 Hz), 7.16 (t, 1, J = 7.6 Hz), 7.40 (t, 2, J = 7.6 Hz), 7.60 (d, 2, J = 8.24 Hz), 7.67 (d, 2), 7.71 (d, 2, J = 8.24 Hz); ^{13}C NMR of one diastereomer: δ = 11.2, 21.9, 52.1, 73.6, 102.2, 118.6, 124.3 ($^1J_{CF}$ = 271 Hz), 124.3, 124.8, 127.6, 128.8, 137.7, 147.8, 148.3, 174.6; HRMS (ESI): [M − H]$^-$ calcd for $C_{21}H_{18}O_4N_2F_3$: 419.122404, found: 419.150434.

2-[(Cyclopropylamino)methyl]-3-[4-(trifluoromethyl)-phenyl]acrylic Acid (5). To resin **1** (40 mg) were added 6 equiv of acetyl chloride (22.2 μL) and 10 equiv of DIEA (89 μL) in 700 μL of CH_2Cl_2. The reaction mixture was shaken for 3 h at room temperature. After the resin was washed, 10 equiv of cyclopropylamine (36.5 μL) and 2 equiv of BEMP (30.1 μL) in 700 μL of DMF were added. The reaction mixture was shaken for 4 h at room temperature and then filtered and washed with DMF, EtOH, CH_2Cl_2, and Et_2O. **5** was cleaved from the resin with 600 μL of CH_2Cl_2/TFA (95:5) in 30 min. After lyophilization from *tert*-BuOH/H_2O, we obtained a crude product with a purity of 87% in analytical HPLC (λ = 214 nm). This was purified by preparative HPLC to obtain 12.2 mg (76% yield): ^{1}H NMR: δ = 0.67/0.75 (m, 4), 2.68 (m, 1), 4.00 (s, 2), 7.72 (d, 2, J = 8.24 Hz), 7.84 (d, 2, J = 8.24 Hz), 8.03; ^{13}C NMR: δ = 3.4, 30.4, 44.1, 124.28 ($^1J_{CF}$ = 271 Hz), 125.5, 126.8, 130.0, 138.0, 143.3, 167.4; HRMS (ESI): [M − H]$^-$ calcd for $C_{14}H_{13}O_2NF_3$: 284.090379, found: 284.089488.

2-[[(Benzoylcyclopropyl)amino]methyl]-3-[4-(trifluoromethyl)phenyl]acrylic Acid (6). To resin **5** (40 mg) were added 5 equiv of benzoic acid (31.7 mg), 5 equiv of PyBroP (121.2 mg) and 10 equiv of DIEA (89 μL) and suspended in 700 μL of CH_2Cl_2/DMF (1:1). After the mixture was shaked for 4 h at room temperature and repetition of the procedure, it was filtered and washed with DMF, EtOH, CH_2Cl_2, and Et_2O. **6** was cleaved from the resin with 600 μL of CH_2Cl_2/TFA (95:5) in 30 min. After lyophilization from *tert*-BuOH/H_2O, we obtained a crude product with a purity of 89% in analytical HPLC (λ = 214 nm). This was analyzed by MS and purified by preparative HPLC to obtain 15.2 mg (75% yield): ^{1}H NMR: δ = 0.18/0.31 (m, 4), 2.46 (m, 1), 4.53 (s, 2), 7.13 (d, 2, J = 7.02 Hz), 7.33 (m, 3), 7.70 (d, 2, 8.24 Hz), 7.76 (d, 2, J = 8.24 Hz), 7.83 (s, 1); ^{13}C NMR: δ = 9.4, 30.8, 43.2, 124.28 ($^1J_{CF}$ = 271 Hz), 125.1, 127.0, 127.7, 129.4, 129.8, 131.3, 137.3, 139.0, 139.2, 168.1, 171.2; HRMS (ESI): [M − H]$^-$ calcd for $C_{21}H_{17}O_3NF_3$: 388.116592, found: 388.113470.

2-[[(4-Brombenzyl)cyclopropylamino]methyl]-3-[4-(trifluoromethyl)pheny]acrylic Acid (7). To resin **5** (40 mg) were added 10 equiv of 4-bromobenzyl bromide (130 mg) and 4 equiv of BEMP (60.2 μL) and suspended in 700 μL of DMF. After the mixture was shaked for 16 h at room temperature, it was filtered and washed with DMF, EtOH, CH_2Cl_2, and Et_2O. **7** was cleaved from the resin with 600 μL of CH_2Cl_2/TFA (95:5) in 30 min. After lyophilization from *tert*-BuOH/H_2O, we obtained a crude product with a purity of 87% in analytical HPLC (λ = 214 nm). **7** was analyzed by MS and purified by preparative HPLC to obtain 18.8 mg (80% yield): ^{1}H NMR: δ = 0.51 (m, 4), 2.06 (m, 1), 3.73 (s, 1), 3.94 (s, 2), 7.27 (d, 2, J = 8.24 Hz), 7.52 (d, 2, J = 8.24

Hz), 7.64 (m, 4), 7.82 (s, 1); ^{13}C NMR: δ = 6.4, 37.0, 50.1, 59.2, 121.4, 124.3 ($^{1}J_{CF}$ = 271 Hz), 125.2, 128.6, 129.1, 130.2, 131.1, 132.6, 138.6, 141.0, 168.6; HRMS (ESI): [M − H]$^-$ calcd for $C_{21}H_{18}O_2NF_3Br$: 452.047838/454.045792, found 452.044660/454.043447.

2-[(Benzenesulfonylcyclopropylamino)methyl]-3-[4-(trifluoromethyl)pheny]acrylic Acid (8). To resin **5** (40 mg) were added 10 equiv of benzenesulfonyl chloride (66.7 mg) and 10 equiv of DIEA (89 μL) and suspended in 700 μL of CH_2Cl_2. After the mixture was shaked for 4 h at room temperature, it was filtered and washed with DMF, EtOH, CH_2Cl_2, and Et_2O. **8** was cleaved from the resin with 600 μL of CH_2Cl_2/TFA (95:5) in 30 min. After lyophilization from *tert*-BuOH/H_2O we obtained a crude product with a purity of 84% in analytical HPLC (λ = 214 nm). This was purified by preparative HPLC to obtain 15.5 mg (70% yield): ^{1}H NMR: δ = 0.61/0.78 (m, 4), 1.62 (m, 1), 4.06 (s, 2), 7.67 (m, 9), 7.8 (s, 1); ^{13}C NMR: δ = 7.4, 31.2, 46.8, 124.3 ($^{1}J_{CF}$ = 271 Hz), 125.2, 127.8, 129.2, 130.3, 130.7, 133.3, 135.1, 138.7, 140.2, 166.1; HRMS (ESI): [M − H]$^-$ calcd for $C_{20}H_{17}NO_4SF_3$: 424.083576, found: 424.080076.

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Supporting Information Available: MS, ^{1}H NMR, and ^{13}C NMR spectra of all products; NOE difference spectra of compounds **2a** and **5a**; HPLC chromatograms of all products and HPLC-MS spectra of compound **3** and **4**. Tables with HPLC purities of the building blocks used in the presented syntheses (39 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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