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New Synthetic Pathway To Diverse 2-Substituted Quinolines Based on a Multicomponent Reaction: Solution-Phase and Solid-Phase Applications

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Using Kobayashi's modification of the Grieco reaction, we were able to synthesize diverse 4-phenylthio-1,2,3,4-tetrahydroquinolines. These intermediates were oxidized and subsequently pyrolized to provide the corresponding quinolines. This new approach to 2-substituted quinolines was exemplified by liquid-phase production of a 25-member library. This was extended to solid-phase chemistry, starting from (L)-4-nitrophenylalanine on Wang resin, for production of a 16-member library. The latter compounds possess potentially interesting VLA-4 antagonist properties.

Introduction

Quinolines and their derivatives represent an important class of organic molecules that attract the interest of both synthetic and medicinal chemists. Substituted quinolines have found applications as pharmaceuticals and agrochemicals as well as general synthetic blocks.

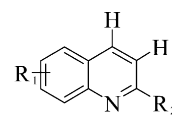
Despite advances in methodologies for the construction of quinoline derivatives, it is still challenging to explore new and efficient synthetic routes, especially for library production and solid-phase applications.

We report here a synthetic pathway to 2-substituted quinolines (Scheme 1) based on a multicomponent reaction (MCR)[1] and its application to library production, both in liquid phase and on solid phase.

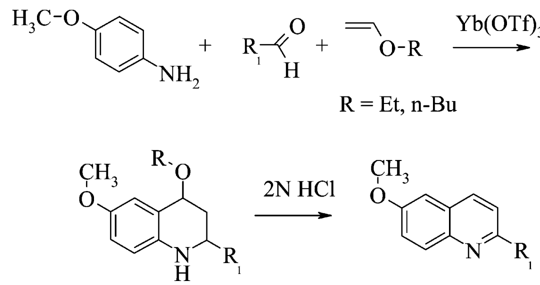
This particular quinoline nucleus is widespread among biologically active compounds, such as antitumor agents,[2] *CysLT* (LTD4) receptor antagonists[3], antileishmanial agents,[4] and HIV-1 replication inhibitors[5] and was recently reported as a scaffold for promising new PDE4 inhibitors.[6] Several syntheses of quinolines bearing different substitution patterns and amenable to small library production using solution phase approaches[7] or solid-phase techniques[8] have been published recently. However, general syntheses of compounds substituted at the 2-position and unsubstituted at the 3- and 4-positions are less common[9] and often suffer from harsh reaction conditions, poor yields, or both. Furthermore, low diversity among the starting materials[2] has limited their use for library production or solid-phase applications.

To overcome these limitations, we turned to the synthesis of tetrahydroquinolines as potential intermediates for the preparation of our target quinoline nucleus. Among the methods available,[10] we were particularly interested in the MCR initially published by Grieco and Bahsas[11] and notably extended by Kobayashi and co-workers.[12] Indeed, this method permits the condensation of anilines, aldehydes, and electron-rich alkenes using lanthanide triflates as Lewis acid catalysts. These mild conditions and the wide variety of available aldehydes and anilines prompted us to explore this approach. Moreover, using enol ethers as the electron-rich alkene, Kobayashi reported the direct formation of the corresponding quinoline as a side product, albeit only in trace amount.[12] However, this side reaction was successfully exploited by others[13,14] to prepare 2-substituted quinolines in good yields but using only *p*-anisidine as starting material (Scheme 2).

Scheme 1



Scheme 2[13,14]



We now report our general approach to diverse 2-substituted quinolines using 1,2,3,4-tetrahydroquinolines as intermediates.

Results and Discussion

Preliminary studies of the imino Diels−Alder reactions were conducted using the model reaction of 2,6-dichlorobenzaldehyde **1** and *p*-toluidine **2** (Scheme 3). These studies showed that, in our hands, using phenylvinyl sulfide **3a** as

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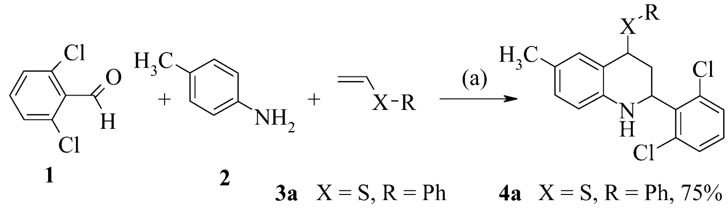
Published on Web 06/26/2004

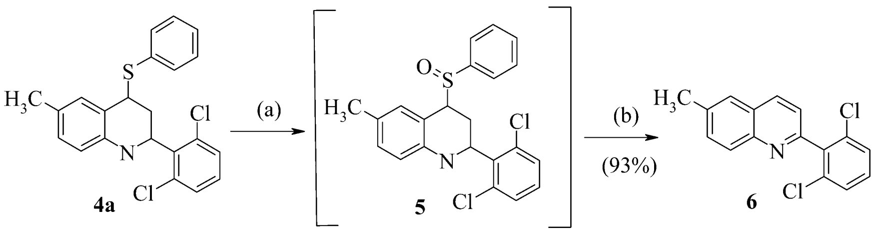
Scheme 3



3a X = S, R = Ph **4a** X = S, R = Ph, 75%
3b X = O, R = n-Bu **4b** X = O, R = n-Bu, 55%
3c X = O, R = t-Bu **4c** X = O, R = t-Bu, product not isolated

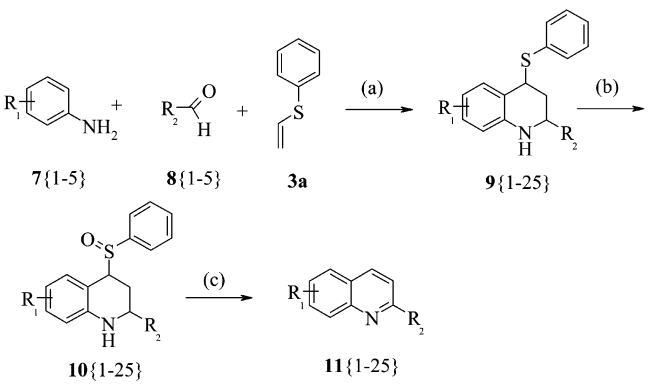
(a) *p*-toluidine (1 equiv), 2,6-dichlorobenzaldehyde (1 equiv), alkene (1.5 equiv), $Yb(OTf)_3$ (0.05 equiv), excess $MgSO_4$, CH_3CN, 16 h, rt.

Scheme 4



(a) $NaIO_4$ (10 equiv), dioxane/water (4:1, v/v), rt, 18 h (b) O_2, dioxane, 80 °C, 18 h.

Scheme 5



(a) aniline (1 equiv), aldehyde (1 equiv), alkene (1.5 equiv), $Yb(OTf)_3$ (0.05 equiv), excess $MgSO_4$, CH_3CN, 18 h, rt. (b) IO_4^- on Amberlyst A-26, dioxane/water (4:1, v/v), 4 h, rt. (c) O_2, dioxane, 18 h, 80 °C.

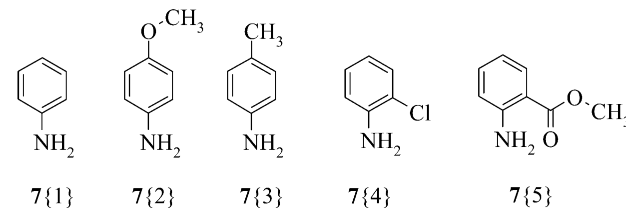


Figure 1. Diversity reagents **7**.

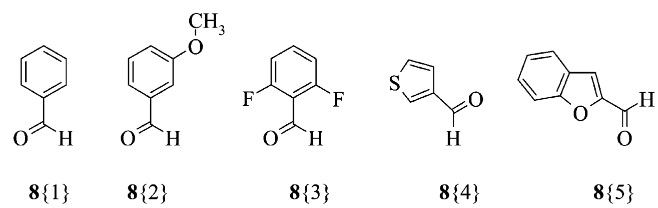


Figure 2. Diversity reagents **8**.

the electron-rich alkene gave consistently higher crude purities and isolated yields of the tetrahydroquinoline **4a**, as compared to enol ethers **3b** or **3c**. We then used this favorable reactivity to establish a new synthetic pathway to 2-substituted quinolines. In doing so, we took advantage of the reactivity of benzylic sulfoxides, most notably thermolysis,[15] allowing aromatization of the tetrahydroquinoline under mild conditions compatible with a solid-phase approach.

To validate this approach, we oxidized the thioether **4a** using an excess of $NaIO_4$ to give the corresponding sulfoxide **5**. The material was used without purification, and direct aromatization effected in the presence of oxygen by simple heating provided quinoline **6**, isolated by flash chromatography in 93% overall yield (Scheme 4).

Several reagents were tested for thioether oxidation, namely *m*-CPBA, Oxone, DMDO, Bu_4NIO_4, and $NaIO_4$. Excess $NaIO_4$ or equimolar *m*-CPBA gave the best results. To simplify the workup procedure, we could efficiently replace $NaIO_4$ with its solid-supported equivalent prepared according to Harrison and Hodge.[16] Using the solution phase sequence depicted in Scheme 5, we extended the generality of this approach by producing a 25-member library.

Thus, anilines **7**{*1−5*} (Figure 1) and aldehydes **8**{*1−5*} (Figure 2) were reacted with phenyl vinyl sulfide **3a** using Kobayashi's protocol[12] to give sulfides **9** (Scheme 5). After liquid−liquid extraction and oxidation in dioxane/water, the sulfoxides **10** were directly pyrolized, after simple polymer filtration, to yield quinolines **11**{*1−25*} (Figure 3). The target compounds were isolated by flash chromatography in overall yields ranging from 8 to 45%, usually with purities higher than 85% as estimated by LC/MS.

Encouraged by these results, we next applied our synthetic pathway to quinolines of interest in our medicinal chemistry programs. For that purpose, we were particularly interested in using (L)-4-aminophenylalanine as the aniline component in the MCR.[17] This approach employed a solid-phase methodology with (L)-4-nitrophenylalanine attached on Wang resin **12**[18] as the starting material (Scheme 6).

Thus, using standard procedures, **12** was deprotected to give **13**, which was acylated with acid chlorides **14**{*1−2*} and DIPEA or coupled with acids **14**{*3−4*} using TBTU and HOBT in the presence of DIPEA to yield **15**. Stannous chloride-mediated reduction of the nitro group of **15** afforded the desired 4-aminophenylalanine derivatives **16**{*1−4*}. The

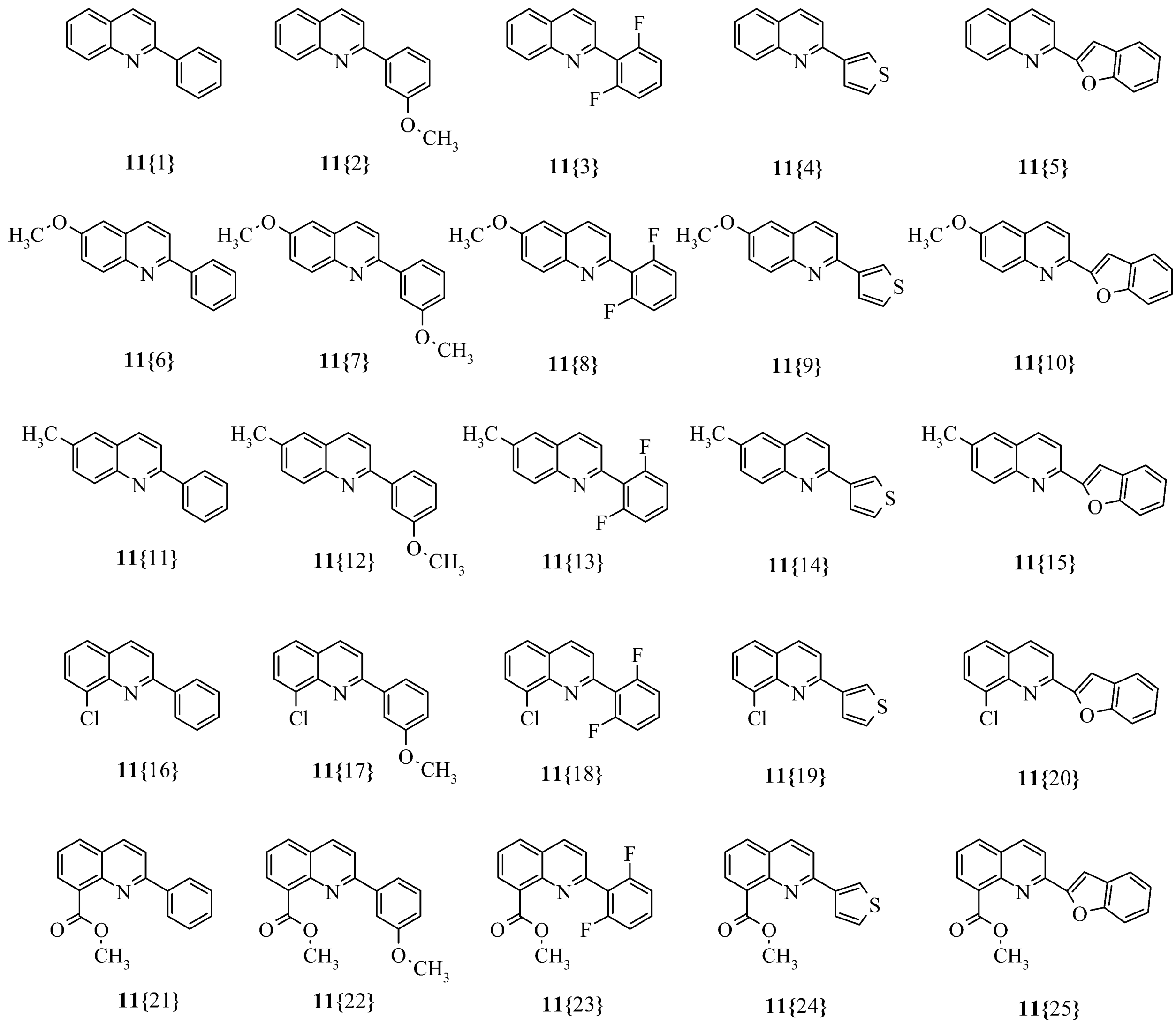


Figure 3. Chemset **11**.

MCR was conducted under conditions similar to those reported by Kiselyov et al.[17] using aldehydes **17**{*1−4*} to afford tetrahydroquinolines **18**{*1−16*}. Due to stability concerns for the intermediates **18** and **19** under the cleavage conditions, we optimized the overall process oxidation/pyrolysis at once. The use of $NaIO_4$ in dioxane/water as the oxidation medium proved inefficient, and attempts to use the more soluble *n*-Bu_4NIO_4 in different swelling organic solvents did not improve the efficacy of the process. Finally, turning to 1.3 equiv of *m*-CPBA in CH_2Cl_2 at room temperature for 4 h followed by the usual washings and pyrolysis of the crude sulfoxide **19** in DMF at 80 °C for 16 h provided the quinolines **20**. The target compounds **21** were obtained by conventional TFA/water (95:5, v/v) cleavage. The overall pathway depicted in Scheme 6 was validated by producing a small library employing acids and acid chlorides **14**{*1−4*} (Figure 4) and aldehydes **17**{*1−4*} (Figure 5) as diversity reagents. The target compounds **21** (Figure 6) were purified by preparative LC/MS. Isolated yields ranged from 18 to 47% with purities ≥95% in all cases. Additionally, no racemization was observed under the reaction conditions employed.[19]

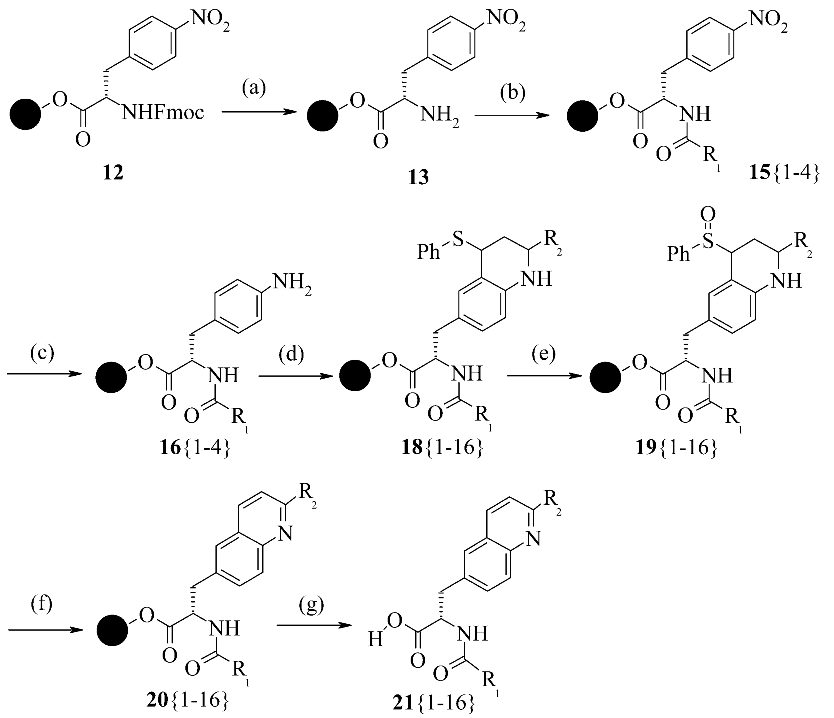
Conclusions

We have established a new methodology, based on a multicomponent reaction, allowing the preparation of diverse 2-substituted quinolines. Derivatives **11** were prepared in solution, and our approach was then extended to solid phase using L-4-nitrophenylalanine **12** as starting material to yield compounds **21**. On the basis of this solid-phase approach, we were able to synthesize a large library of derivatives **21** that were screened in different in vitro assays. Several members displayed high potency as VLA-4 antagonists;[20] these are potentially useful for the treatment of inflammatory diseases and are currently under study in our laboratories.

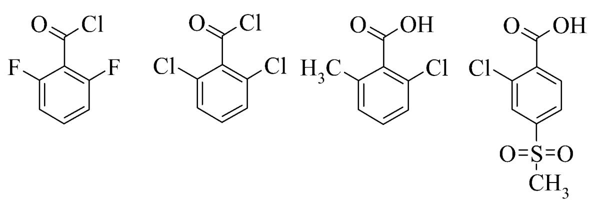
Experimental Section

General Information. All solvents and reagents were obtained from commercial sources and used without further purification. Parallel syntheses were performed using a Quest 210 synthesizer from Argonaut Technologies. ^1H NMR spectra were recorded on a 250- or 400-MHz spectrometer. Chemical shifts are expressed in parts per million (δ) from TMS. Analytical HPLC was performed using an Agilent 1100 series HPLC system mounted with an INERTSIL ODS 3 C18, DP 5-μm, 250 × 4.6 mm column.

Scheme 6

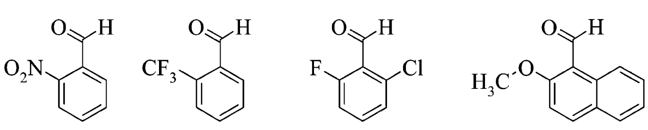


(a) 20% piperidine, DMF, rt, 0.5 h. (b) R_1COCl **14**{1−2} (5 equiv), DIPEA (5 equiv), CH_2Cl_2, rt, 16 h or R_1COOH **14**{3−4} (5 equiv), TBTU (5 equiv), HOBT (5 equiv), DIPEA (15 equiv), DMF, rt, 16 h. (c) $SnCl_2$ 2 M, DMF, rt, 16 h. (d) R_2CHO **17**{*1−4*}(10 equiv), $PhSCHCH_2$ (10 equiv), $Yb(OTf)_3$ (0.05 equiv), CH_3CN/CH_2Cl_2 (2:1, v/v), rt, 16 h. (e) mCPBA (1.3 equiv), CH_2Cl_2, rt, 4 h. (f) O_2, DMF, 80 °C, 16 h. (g) TFA/H_2O (95:5, v/v), rt, 2 × 0.5 h.



14{1} **14**{2} **14**{3} **14**{4}

Figure 4. Diversity reagents **14**.



17{1} **17**{2} **17**{3} **17**{4}

Figure 5. Diversity reagents **17**.

Analytic mass spectrometric measurements in LC/MS mode were performed as follows:

1. HPLC Conditions. An Agilent 1100 series HPLC system mounted with an INERTSIL ODS 3 C18, DP 5-μm, 250 × 4.6 mm column. The chromatography was carried out at 35 °C. The gradient ran from 100% solvent A (acetonitrile, water, TFA (10/90/0.1, v/v/v)) to 100% solvent B (acetonitrile, water, TFA (90/10/0.1, v/v/v)) in 7 min with a hold at 100% B of 4 min. The flow rate was set at 2.5 mL/min, and a split of 1/25 was used just before the API source.

2. MS Conditions. Samples were dissolved in acetonitrile/water, 70/30, v/v at a concentration of ∼250 μg/mL. API spectra (+ or −) were performed using a Finnigan (San Jose, CA) LCQ ion trap mass spectrometer. The APCI source was operated at 450 °C, and the capillary heater, at 160 °C. The ESI source was operated at 3.5 kV, and the capillary heater, at 210 °C.

Preparative purification in LC/MS mode was performed as follows:

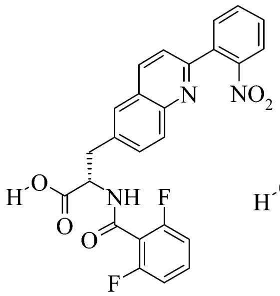
3. HPLC Conditions. A Waters Prep 4000 HPLC system was connected to a Waters 996 PDA, and the chromatography was carried out at room temperature with a flow of 35 mL/min. Acidic gradient on a YMC CombiPrep ODS-AQ: 50 × 20 mm ID 5 μm column and 10 × 20 mm i.d. precolumn (Table 1).

4. MS Conditions. Samples were dissolved in acetonitrile/water, 70/30, v/v, with the concentration depending on the solubility of the sample. ESI spectra were performed using an LCZ, Waters Micromass MS Technologies operated under Masslynx 4.0, sp1. The ESI source operated at 3.5 kV; cone, 25 V; source temp, 150 °C; desolvation temp, 300 °C; desolvation gas, 530 L/h.

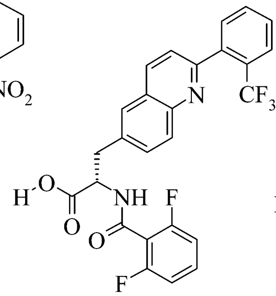
Chiral HPLC was performed on Chiralpak AD 250 × 4.6 mm 5-μm (Chiral Technologies Europe, Lot No. AD00CE-JG170) using ethanol/isohexane/diethylamine (50/50/0.1) as eluent. The flow rate was set at 1 mL/min. The operating temperature was 30 °C, and UV detection was performed at 220 nm.

Flash chromatography was performed on silica gel 60 (E. Merck) 230−400 mesh ASTM. Thin-layer chromatography (TLC) was performed on 0.2-mm silica gel 60 F_{254} plates (E. Merck).

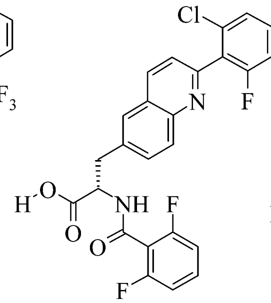
General Procedure for the Synthesis of 4-Substituted 2-(2′,6′-Dichlorophenyl)-6-methyl-tetrahydroquinolines 4a−c. In three reactors, a solution of 175 mg (1 mmol, 1 equiv) of 2,6-dichlorobenzaldehyde **1** and 108 mg (1 mmol, 1 equiv)



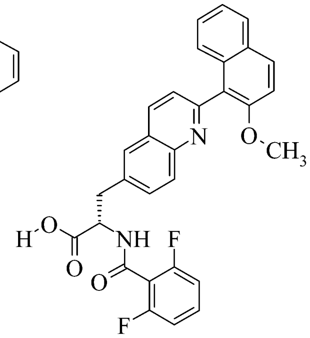
21{1}
66 mg (36%)



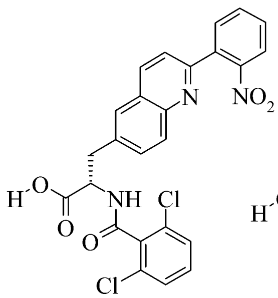
21{2}
58 mg (31%)



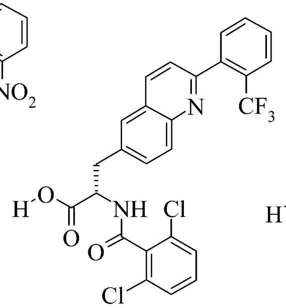
21{3}
63 mg (34%)



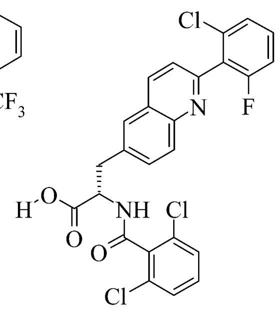
21{4}
35 mg (18%)



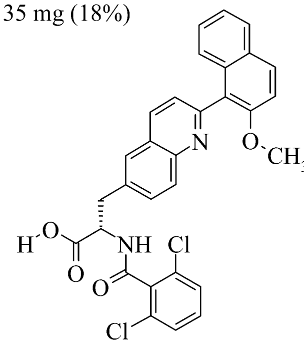
21{5}
71 mg (37%)



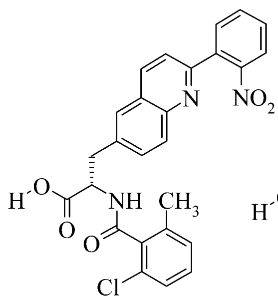
21{6}
69 mg (34%)



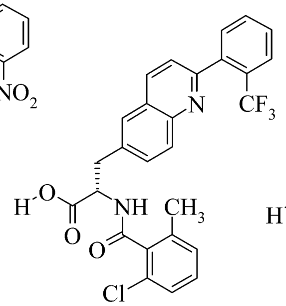
21{7}
90 mg (46%)



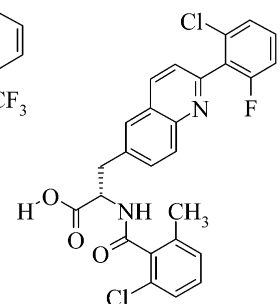
21{8}
47 mg (23%)



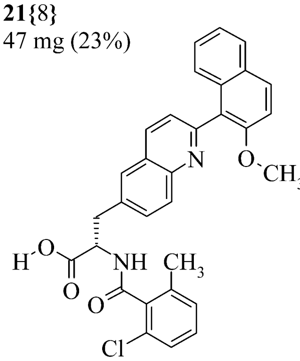
21{9}
62 mg (34%)



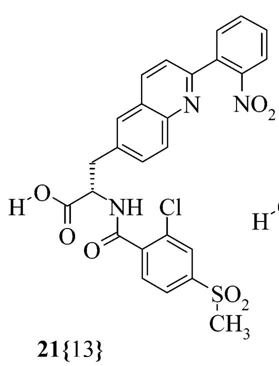
21{10}
88 mg (45%)



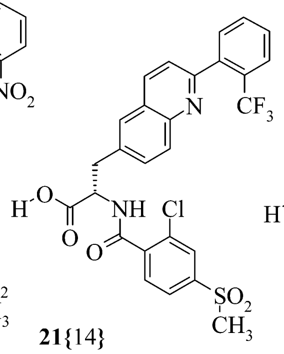
21{11}
88 mg (47%)



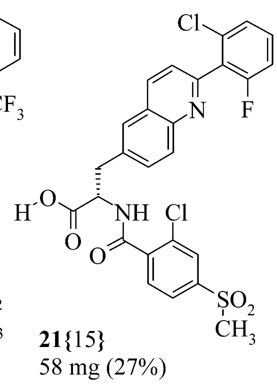
21{12}
36 mg (18%)



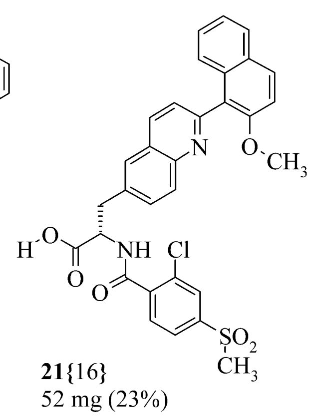
21{13}
75 mg (37%)



21{14}
70 mg (32%)



21{15}
58 mg (27%)



21{16}
52 mg (23%)

Figure 6. Chemset **21**.

of *p*-toluidine **2** in 1.5 mL of CH_2Cl_2 was prepared. A 250-mg portion of $MgSO_4$ was added to each reactor, and the resulting suspensions were agitated at room temperature for 1 h. After this time, 31 mg (0.05 mmol, 0.05 equiv) of Yb-$(OTf)_3$ in 3 mL of CH_3CN and, finally, 271 μL of **3a**, 194 μL of **3b**, or 197 μL of **3c** (1.5 mmol, 1.5 equiv) were added while stirring. The resulting mixtures were agitated at room temperature for 16 h. Insolubles were filtered over Celite, and the resulting crudes were diluted with 5% aq $NaHCO_3$ (10 mL). Each aqueous phase was extracted three times with AcOEt (5 mL/extraction). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and evaporated. The resulting crudes were purified by flash chromatography over silica gel.

2-(2,6-Dichlorophenyl)-4-phenylthio-1,2,3,4-tetrahydroquinoline, 4a. 300 mg; yield, 75%. Mixture of two diastereomers (6/4); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.89−1.97 (m, 0.4H), 2.2−2.3 (m, 3.6H), 2.68−2.85 (m, 1H), 4.51−

Table 1 [a]

time (min)	A%	B%	C%
0	90	0	10
6	0	90	10
8	0	90	10
8.5	90	0	10
10.5	90	0	10

[a] With A, water; B, acetonitrile; C, $H_2O/CH_3CN/TFA$ 50/50/1.

4.61 (m, 1H), 5.37 (dd, J = 12 Hz, J = 3.5 Hz, 0.6H), 5.93 (dd, J = 12 Hz, J = 3.5 Hz, 0.4H), 6.42−6.5 (m, 1H), 6.85−6.92 (m, 1H), 7.08−7.58 (m, 4H). R_f = 0.5 (hexane/AcOEt, 9/1, v/v).

2-(2,6-Dichlorophenyl)-4-*n*-butoxy-1,2,3,4-tetrahydroquinoline, 4b. 201 mg; yield, 55%. Mixture of two diastereomers (9/1); ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.96 (t, J = 7.3 Hz, 3H), 1.34−1.74 (m, 4H), 2.21−2.3 (m, 4H), 2.46−2.58 (m, 1H), 3.51−3.63 (m, 1H), 3.66−3.76 (m, 1H), 4.68 (dd, J = 10.7 Hz, J = 5 Hz, 1H), 5.45 (dd, J = 12.5 Hz, J = 3.5 Hz, 1H), 6.41 (d, J = 8.1 Hz, 1H), 6.86 (bd, J = 8.1 Hz), 7.13 (t, J = 7.9 Hz, 1H), 7.23 (bs, 1H), 7.31 (d, J = 7.9 Hz, 1H). R_f = 0.55 (hexane/AcOEt, 9/1, v/v).

2-(2,6-Dichlorophenyl)-4-*tert*-butoxy-1,2,3,4-tetrahydroquinoline, 4c. Complex crude mixture; products not purified.

2-(2′,6′-Dichlorophenyl)-6-methyl-quinoline, 6. To a solution of 401 mg (1 mmol, 1 equiv) of thioether **4a** in dioxane/water (4:1, v/v, 10 mL) was added 2.2 g of $NaIO_4$ (10 mmol, 10 equiv). The resulting suspension was stirred for 18 h at room temperature. The crude was diluted with 5% aq $NaHCO_3$ (100 mL) and extracted two times with AcOEt (2 × 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and evaporated. The resulting crude mixture was dissolved in dioxane (10 mL) and heated at 80 °C for 18 h. The solvent was evaporated, and the resulting crude material was purified by flash chromatography over silica gel (hexane/AcOEt, 4:1, v/v) to yield **6**.

2-(2,5-Dichlorophenyl)-6-methyl-quinoline, 6. 271 mg; yield, 93%. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.57 (s, 3H), 7.24−7.45 (m, 4H), 7.58 (dd, J = 8.6 Hz, J = 1.9 Hz, 1H), 7.58 (bs, 1H), 8.07 (d, J = 8.6 Hz), 8.16 (d, J = 8.4 Hz). R_f = 0.43 (hexane/AcOEt, 4/1, v/v).

General Procedure for the Synthesis of 2-Substituted Quinolines 11{*1*−*25*}. To aniline **7** (1 mmol, 1 equiv) was added aldehyde **8** (1 mmol, 1 equiv) in 1.5 mL of CH_2Cl_2 with $MgSO_4$ (250 mg). To the resulting suspension was added $Yb(OTf)_3$ (31 mg, 0.05 mmol, 0.05 equiv) in 3 mL of CH_3CN and phenyl vinyl sulfide (271 μL, 1.5 mmol, 1.5 equiv). The resulting slurries were agitated 18 h at room temperature. After this time, the insolubles were filtered, and the solvents were removed under vacuum. To the resulting crudes was added 5 mL of a 5% (w/v) aqueous $NaHCO_3$ solution. The aqueous phases were extracted three times with 4 mL of AcOEt. The organic phases were combined and evaporated under vacuum. The resulting crudes were solubilized in 1,4-dioxane (4 mL), and to these solutions were added IO_4^- on Amberlyst (1.2 g, 1.5 mmol, 1.5 equiv) and 1 mL of water. After 4 h of agitation at room temperature, the resin was filtered, and the resulting solutions were heated at 80 °C for 18 h. The crudes were dried and purified by MPLC on silica gel.

2-Phenylquinoline 11{1}. 48 mg (23%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.44−7.57 (m, 4H), 7.68−7.77 (m, 1H), 7.82 (dd, J = 8.1 Hz, J = 1.1 Hz, 1H), 7.87 (d, J = 8.55 Hz, 1H), 8.12−8.19 (m, 3H), 8.21 (d, J = 8.55 Hz, 1H). LC/MS m/z: 206 $[M + H]^+$.

2-(3-Methoxyphenyl)quinoline 11{2}. 70 mg (29%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.93 (s, 3H), 7.01 (ddd, J = 8.2 Hz, J = 2.6 Hz, J = 1.0 Hz, 1H), 7.43 (dd, J = 8.2 Hz, J = 8.1 Hz, 1H), 7.52 (ddd, J = 8.2 Hz, J = 1.2 Hz, J = 1.0 Hz, 1H), 7.67−7.83 (m, 4H), 7.85 (d, J = 8.5 Hz, 1H), 8.14−8.24 (m, 2H). LC/MS m/z: 236 $[M + H]^+$.

2-(2,5-Difluorophenyl)quinoline 11{3}. Isolated with unsatisfactory purity.

2-([3]Thienyl)quinoline 11{4}. 91 mg (43%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.43 (dd, J = 5 Hz, J = 2.9 Hz, 1H), 7.49 (m, 1H), 7.70 (m, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.78 (dd, J = 8.4 Hz, J = 1.2 Hz, 1H), 7.88 (dd, J = 5 Hz, J = 1.4 Hz, 1H), 8.04 (dd, J = 2.9 Hz, J = 1.2 Hz, 1H), 8.15−8.25 (m, 2H). LC/MS m/z: 212 $[M + H]^+$.

2-Benzofuran-2-yl-quinoline 11{5}. 53 mg (21%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.25−7.41 (m, 2H), 7.49−7.57 (m, 1H), 7.61 (bs, 1H), 7.63−7.78 (m, 3H), 7.82 (dd, J = 8.1 Hz, J = 1.2 Hz, 1H), 8.1 (d, J = 8.7 Hz, 1H), 8.16−8.26 (m, 2H). LC/MS m/z: 246 $[M + H]^+$.

2-Phenyl-6-methoxyquinoline 11{6}. 79 mg (33%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.94 (s, 3H), 7.08 (bd, J = 2.7 Hz, 1H), 7.38 (dd, J = 9.2 Hz, J = 2.7 Hz, 1H), 7.41−7.55 (m, 3H), 7.82 (d, J = 8.55 Hz, 1H), 8.01−8.18 (m, 4H). LC/MS m/z: 236 $[M + H]^+$.

2-(3-Methoxyphenyl)-6-methoxyquinoline 11{7}. 73 mg (27%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.92 (s, 3H), 3.94 (s, 3H), 6.99 (ddd, J = 8.2 Hz, J = 2.6 Hz, J = 0.8 Hz, 1H), 7.08 (d, J = 2.7 Hz, 1H), 7.38 (dd, J = 9.2 Hz, J = 2.7 Hz, 1H), 7.41 (dd, J = 7.8 Hz, J = 8.1 Hz, 1H), 7.67 (bd, J = 7.8 Hz, 1H), 7.74 (bs, 1H), 7.81 (d, J = 8.7 Hz, 1H), 8.07 (d, J = 9.1 Hz, 1H), 8.09 (d, J = 8.7 Hz, 1H). LC/MS m/z: 266 $[M + H]^+$.

2-(2,5-Difluorophenyl)-6-methoxyquinoline 11{8}. 57 mg (21%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.95 (s, 3H), 6.96−7.09 (m, 2H), 7.12 (d, J = 2.75 Hz, 1H), 7.3−7.41 (m, 1H), 7.4 (dd, J = 9.2 Hz, J = 2.75 Hz, 1H), 7.52 (bd, J = 8.4 Hz, 1H), 8.07 (d, J = 9.3 Hz, 1H), 8.13 (d, J = 8.5 Hz, 1H). LC/MS m/z: 272 $[M + H]^+$.

2-([3]Thienyl)-6-methoxyquinoline 11{9}. 83 mg (34%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.93 (s, 3H), 7.06 (d, J = 2.75 Hz, 1H), 7.36 (dd, J = 9.2 Hz, J = 2.75 Hz, 1H), 7.42 (dd, J = 5 Hz, J = 2.9 Hz, 1H), 7.72 (d, J = 8.55 Hz, 1H), 7.84 (dd, J = 5 Hz, J = 1.2 Hz, 1H), 7.97 (dd, J = 2.9 Hz, J = 1.2 Hz, 1H), 7.98−8.08 (m, 2H). LC/MS m/z: 242 $[M + H]^+$.

2-Benzofuran-2-yl-6-methoxyquinoline 11{10}. 46 mg (16%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.94 (s, 3H), 7.07 (d, J = 2.75 Hz, 1H), 7.22−7.44 (m, 3H), 7.52 (s, 1H), 7.58−7.7 (m, 2H), 7.96 (d, J = 8.55 Hz, 1H), 8.09 (d, J = 9.2 Hz, 1H), 8.11 (d, J = 8.55 Hz, 1H). LC/MS m/z: 276 $[M + H]^+$.

2-Phenyl-6-methylquinoline 11{11}. 85 mg (39%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.54 (s, 3H), 7.40−7.56 (m, 4H), 7.57 (bs, 1H), 7.82 (d, J = 8.55 Hz, 1H), 8.06 (d, J = 8.55 Hz, 1H), 8.08−8.20 (m, 3H). LC/MS m/z: 220 [M + H]$^+$.

2-(3-Methoxyphenyl)-6-methylquinoline 11{12}. 88 mg (35%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.54 (s, 3H), 3.92 (s, 3H), 6.99 (ddd, J = 8.2 Hz, J = 2.7 Hz, J = 0.9 Hz, 1H), 7.37−7.46 (m, 1H), 7.51−7.60 (m, 2H), 7.66−7.71 (m, 1H), 7.75 (bs, 1H), 7.81 (d, J = 8.55 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.55 Hz, 1H). LC/MS m/z: 250 [M + H]$^+$.

2-(2,5-Difluorophenyl)-6-methylquinoline 11{13}. 91 mg (35%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.56 (s, 3H), 6.97−7.09 (m, 2H), 7.37 (tt, J = 8.4 Hz, J = 6.4 Hz, 1H), 7.52 (d, J = 8.55 Hz, 1H), 7.58 (dd, J = 8.7 Hz, J = 1.8 Hz, 1H), 7.63 (bs, 1H), 8.07 (d, J = 8.7 Hz, 1H), 8.15 (d, J = 8.55 Hz, 1H). LC/MS m/z: 256 [M + H]$^+$.

2-([3]Thienyl)-6-methylquinoline 11{14}. 81 mg (36%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.53 (s, 3H), 7.42 (dd, J = 5.0 Hz, J = 2.9 Hz, 1H), 7.49−7.57 (m, 2H), 7.72 (d, J = 8.5 Hz, 1H), 7.86 (dd, J = 5.0 Hz, J = 1.2 Hz, 1H), 7.95−8.05 (m, 2H), 8.06 (d, J = 8.5 Hz, 1H). LC/MS m/z: 226 [M + H]$^+$.

2-Benzofuran-2-yl-6-methylquinoline 11{15}. 115 mg (44%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.54 (s, 3H), 7.24−7.40 (m, 2H), 7.54−7.60 (m, 3H), 7.61−7.70 (m, 2H), 7.97 (d, J = 8.55 Hz, 1H), 8.06−8.17 (m, 2H). LC/MS m/z: 260 [M + H]$^+$.

2-Phenyl-8-chloroquinoline 11{16}. Isolated with unsatisfactory purity.

2-(3-Methoxyphenyl)-8-chloroquinoline 11{17}. 77 mg (28%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.94 (s, 3H), 7.03 (ddd, J = 8.2 Hz, J = 2.6 Hz, J = 0.8 Hz, 1H), 7.37−7.49 (m, 2H), 7.74 (dd, J = 8.1 Hz, J = 1.2 Hz, 1H), 7.78−7.87 (m, 2H), 7.91−7.99 (m, 2H), 8.22 (d, J = 8.7 Hz, 1H). LC/MS m/z: 270 [M + H]$^+$.

2-(2,5-Difluorophenyl)-8-chloroquinoline 11{18}. 33 mg (12%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.97−7.12 (m, 2H), 7.31−7.46 (m, 1H), 7.5 (dd, J = 8.2 Hz, J = 7.5 Hz, 1H), 7.61−7.7 (m, 1H), 7.79 (dd, J = 8.2 Hz, J = 1.2 Hz, 1H), 7.87 (dd, J = 7.5 Hz, J = 1.2 Hz, 1H), 8.26 (d, J = 8.55 Hz, 1H). LC/MS m/z: 276 [M + H]$^+$.

2-([3]Thienyl)-8-chloroquinoline 11{19}. 48 mg (19%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.35−7.47 (m, 2H), 7.7 (dd, J = 8.1 Hz, J = 1.2 Hz, 1H), 7.78−7.85 (m, 2H), 7.96 (dd, J = 5.2 Hz, J = 1.2 Hz, 1H), 8.13 (dd, J = 2.9 Hz, J = 1.2 Hz, 1H), 8.16 (d, J = 8.7 Hz, 1H). LC/MS m/z: 246 [M + H]$^+$.

2-Benzofuran-2-yl-8-chloroquinoline 11{20}. 54 mg (19%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.3 (dd, J = 7.5 Hz, J = 1 Hz, 1H), 7.33−7.47 (m, 2H), 7.58−7.64 (m, 1H), 7.66−7.79 (m, 3H), 7.85 (dd, J = 7.5 Hz, J = 1.4 Hz, 1H), 8.10 (d, J = 8.55 Hz, 1H), 8.24 (d, J = 8.55 Hz, 1H). LC/MS m/z: 280 [M + H]$^+$.

2-Phenylquinoline-8-carboxylic Acid Methyl Ester 11{21}. 60 mg (23%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.09 (s, 3H), 7.41−7.59 (m, 4H), 7.87−7.99 (m, 2H), 8.04 (dd, J = 7.2 Hz, J = 1.5 Hz, 1H), 8.19−8.3 (m, 3H). LC/MS m/z: 264 [M + H]$^+$.

2-(3-Methoxyphenyl)quinoline-8-carboxylic Acid Methyl Ester 11{22}. 58 mg (20%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.93 (s, 3H), 4.09 (s, 3H), 7.02 (ddd, J = 8.2 Hz, J = 2.6 Hz, J = 0.8 Hz, 1H), 7.42 (dd, J = 8.1 Hz, J = 7.9 Hz, 1H), 7.53 (dd, J = 8.1 Hz, J = 7.9 Hz, 1H), 7.75−7.83 (m, 1H), 7.88−7.98 (m, 3H), 8.04 (dd, J = 7.2 Hz, J = 1.4 Hz, 1H), 8.22 (d, J = 8.7 Hz, 1H). LC/MS m/z: 294 [M + H]$^+$.

2-(2,5-Difluorophenyl)quinoline-8-carboxylic Acid Methyl Ester 11{23}. 40 mg (13%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.09 (s, 3H), 7.03 (m, 2H), 7.38 (m, 1H), 7.6 (dd, J = 8.2 Hz, J = 7.2 Hz, 1H), 7.63−7.7 (m, 1H), 7.97 (dd, J = 8.2 Hz, J = 1.4 Hz, 1H), 8.03 (dd, J = 7.2 Hz, J = 1.4 Hz, 1H), 8.25 (d, J = 8.5 Hz, 1H). LC/MS m/z: 300 [M + H]$^+$.

2-([3]Thienyl)quinoline-8-carboxylic Acid Methyl Ester 11{24}. 67 mg (25%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.08 (s, 3H), 7.42 (dd, J = 5 Hz, J = 2.9 Hz, 1H), 7.5 (dd, J = 8.1 Hz, J = 7.2 Hz, 1H), 7.81 (d, J = 8.55 Hz, 1H), 7.86−7.93 (m, 2H), 8.02 (dd, J = 7.2 Hz, J = 1.5 Hz, 1H), 8.08 (dd, J = 3 Hz, J = 1.2 Hz, 1H), 8.17 (d, J = 8.55 Hz, 1H). LC/MS m/z: 270 [M + H]$^+$.

2-Benzofuran-2-yl-quinoline-8-carboxylic Acid Methyl Ester 11{25}. 109 mg (36%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.12 (s, 3H), 7.27−7.41 (m, 2H), 7.49−7.64 (m, 2H), 7.65−7.74 (m, 2H), 7.93 (dd, J = 8.3 Hz, J = 1.4 Hz, 1H), 8.07 (dd, J = 7.3 Hz, J = 1.5 Hz, 1H), 8.11 (d, J = 8.55 Hz, 1H), 8.26 (d, J = 8.55 Hz, 1H). LC/MS m/z: 304 [M + H]$^+$.

General Procedure for the Synthesis of Quinolines 21{*1−16*}. Resin **12** (8 g, 6 mmol) was washed three times with DMF (80 mL/washing). It was then shaken in a piperidine/DMF (4:1, v/v) solution (80 mL) for 5 min at room temperature, filtered, and shaken a second time for 15 min at room temperature in the same solution (80 mL), then it was filtered and washed (80 mL/washing): 6 × DMF, 3 × CH_2Cl_2, 3 × MeOH, 3 × CH_2Cl_2, 3 × DMF. The resin was swelled in DMF/CH_2Cl_2, 2:1, v/v (up to a total volume of 80 mL) and divided into four equal parts, which were filtered. Two parts were treated with 5 equiv (7.5 mmol) of an acid chloride **14**{*1−2*} in 20 mL of CH_2Cl_2 and 5 equiv of DIPEA (1.3 mL, 7.5 mmol). Alternatively, the two remaining parts were treated with 5 equiv (7.5 mmol) of an acid **14**{*3−4*}, 5 equiv of TBTU (2.4 g, 7.5 mmol), 5 equiv fo HOBT (1 g, 7.5 mmol), and 15 equiv of DIPEA (3.9 mL, 22.5 mmol) in 20 mL DMF. The resulting slurries were shaken for 16 h at room temperature, and a negative Chloranil[21] test showed complete reactions in each case. Each of the resins **15**{*1−4*} was filtered and washed (20 mL/washing): 6 × DMF, 3 × CH_2Cl_2, 3 × DMF, 3 × CH_2Cl_2, 3 × MeOH, 3 × DMF. Resins **15**{*1−4*} were swelled in 20 mL of a 2 M solution of $SnCl_2$ in DMF and shaken for 16 h at room temperature to give resins **16**{*1−4*}. The latter were filtered and washed (20 mL/washing): 3 × DMF, 3 × (CH_2Cl_2/Et_3N, 9:1, v/v), 3 × DMF, 3 × CH_2Cl_2, 3 × MeOH, 3 × DMF. Each resin **16**{*1−4*} was swelled in DMF/CH_2Cl_2, 2:1, v/v (up to a total volume of 20 mL) and divided into four equal parts, which were filtered and washed 3 × CH_2Cl_2 (10 mL/washing). To each resin was added an aldehyde **17**{*1−4*} (3.75 mmol, 10 equiv) in 2 mL of CH_2Cl_2/CH_3CN (1:2, v/v), $Yb(OTf)_3$ (12 mg, 0.02 mmol) in 2 mL of CH_2Cl_2/CH_3CN (1:2, v/v), and finally, phenyl vinylsulfide (680 μL, 3.75 mmol, 10 equiv). The resulting suspensions were shaken at room temperature for 18 h. Resins **18**{*1−16*} were then filtered and washed (10 mL/washing): 3 × CH_2Cl_2, 3 × DMF, 3 × CH_2Cl_2, 3 × MeOH, and 3 × CH_2Cl_2. To the resins was added a solution of *m*-CPBA (84 mg, 0.49 mmol, 1.3 equiv) in 5 mL of CH_2Cl_2. The resulting slurries were shaken at room temperature for 4 h. Resins **19**{*1−16*} were filtered and washed (3 × CH_2Cl_2, 3 × DMF) and subsequently swelled in 5 mL of DMF and shaken at 80 °C for 16 h. Resins **20**{*1−16*} were washed (5 mL/washing) (3 × DMF, 3 × CH_2Cl_2, 3 × MeOH) and dried under high vacuum. The target compounds were obtained by cleavage in a 95:5, v/v solution of TFA/H_2O (5 mL, 2 × 30 min) and were purified by preparative LC/MS.

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Supporting Information Available. ^{1}H NMR, LC/MS profiles of the members of chemsets **11** and **21**. Chiral HPLC studies[19] for **21**{*1*}, **21**{*6*}, **21**{*11*}, and **21**{*16*}. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Aliquots of some randomly chosen compounds **21** were esterified using excess $SOCl_2$ in refluxing MeOH, coevaporated several times with toluene, and dried under high vacuum. Each crude was then divided into two portions. The first portions were analyzed by chiral HPLC. The second portions were epimerized using PS-TBD in refluxing MeOH to yield mixtures of enantiomers that were in turn analyzed by chiral HPLC after resin filtration. All the methyl esters thus obtained were found to be homogeneous by LC/MS. For the chiral HPLCs recorded, see the Supporting Information.

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