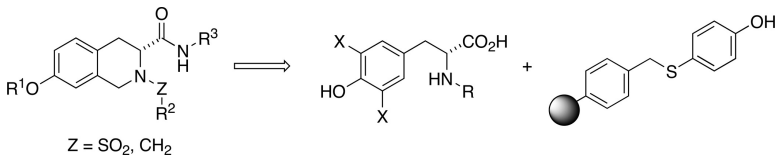
Article

Solid-Phase Synthesis of 1,2,3,4-Tetrahydroisoquinoline Derivatives Employing Support-Bound Tyrosine Esters in the Pictet–Spengler Reaction

Timothy R. Kane, Cuong Q. Ly, Daphne E. Kelly, and Jeffrey M. Dener

J. Comb. Chem., **2004**, 6 (4), 564-572• DOI: 10.1021/cc020105t • Publication Date (Web): 19 June 2004



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 1 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Solid-Phase Synthesis of 1,2,3,4-Tetrahydroisoquinoline Derivatives Employing Support-Bound Tyrosine Esters in the Pictet−Spengler Reaction

Timothy R. Kane, Cuong Q. Ly, Daphne E. Kelly, and Jeffrey M. Dener*

Discovery Partners International, ChemRx Division, 385 Oyster Point Boulevard, Suite 1, South San Francisco, California 94080

Received November 22, 2002

The solid-phase synthesis of 1,2,3,4-tetrahydroisoquinoline-3-carboxamides employing carboxyl-supported, *o*-alkylated tyrosine esters in a Pictet−Spengler reaction is described. Esterification of [4-(hydroxyphenyl)-thiomethyl]polystyrene (Marshall resin) with ethers of *N*-BOC-L-tyrosine using diisopropylcarbodiimide (DIC) and 4-dimethylaminopyridine (4-DMAP) afforded the solid-supported ester derivatives. Removal of the BOC group with trifluoroacetic acid (TFA) afforded the carboxyl-supported tyrosine ester, which was then treated with paraformaldehyde and TFA to afford the desired solid-supported counterpart. Acylation of the secondary amine with arylsulfonyl chlorides followed by reaction with amines resulted in the formation of the desired 2-arylsulfonyl-7-alkoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamides. Alternatively, the support-bound tetrahydroisoquinoline-3-carboxylate derivatives could be treated with an aldehyde and a reducing agent to give the corresponding support-bound tertiary amine. Exposure of these resin-bound products to amines afforded the corresponding 2-alkyl-7-alkoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamides after cleavage from the resin. Alternative routes to the desired chemotypes, as well optimization of the conditions for the Pictet−Spengler reaction and the conditions for the acylation and reductive amination of the support-bound secondary amines, are also described.

Introduction

Solid-phase organic chemistry has become an essential tool to the practicing synthetic and medicinal chemist with the acceptance of combinatorial chemistry as an integral technology for drug discovery.[1] The development and execution of various organic reactions on supports has become a primary focus of many researchers seeking to expand the repertoire of synthetic reactions to ultimately provide novel chemotypes available via solid-phase synthesis. Carbon−carbon-forming reactions[2] and heterocycle syntheses[3] represent two important examples of these areas of interest. As part of a program to generate combinatorial libraries for drug discovery and lead optimization, we developed a synthesis of tetrahydroisoquinolines using a support-bound tyrosine ether that relies upon the Pictet−Spengler reaction (Scheme 1).[4,5] Our choice of solid support, [4-(hydroxyphenyl)thiomethyl]polystyrene (Marshall resin, **6)**, was based on our previous experience, whereby esters derived from **6** produced carboxamides after treatment of the carboxyl-supported esters with amines with concurrent liberation of the desired product from the resin. This resin is compatible with other reaction conditions such as acid-mediated deprotection and reductive amination.[6] Herein, we demonstrate that this resin is compatible with the strong acid necessary to effect the Pictet−Spengler reaction of a carboxyl-supported *N*-BOC-tyrosine ester to generate the tetrahydroisoquinoline ring system. In addition, we were able to prepare 7-alkoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxamide derivatives **1**−**3** containing three points of diversity.

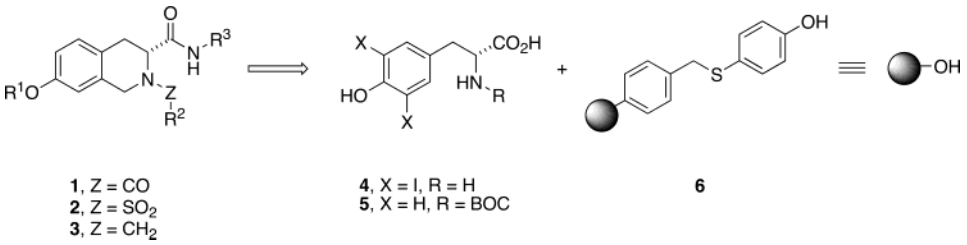
As shown in Scheme 2, our initial route to compounds **1**−**3** revolved around the solution-phase preparation of the tetrahydroisoquinoline nucleus, followed by attachment to resin **6**. Starting from commercially available *N*-BOC-3,5-diiodo-L-tyrosine (**4**), 7-hydroxy-1,2,3,4-tetrahydroisoquinoline derivative **8** was prepared according to a literature report[7] and alkylated to afford 7-alkoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **9**.[8] Attachment of acid **9** to resin **6** afforded BOC-protected tetrahydroisoquinoline ester **10**. Removal of the BOC group with trifluoroacetic acid, followed by acylation of the resulting amine salt with either acid chlorides or sulfonyl chlorides in the presence of a base, afforded amide **11** or sulfonamide **12**. Treatment of resin **11** or **12** with an amine afforded **1** or **2** upon amide formation and liberation from the resin (Scheme 2).

Although the solid-phase synthesis shown in Scheme 2 proceeded smoothly to cleanly afford the desired products, the synthesis of tetrahydroisoquinoline ethers **9** on a scale sufficient to allow for the facile preparation of a 5000-member library was problematic. The solution-phase Pictet−Spengler reaction and BOC protection to prepare **7** proceeded satisfactorily as reported in the literature. Whereas the yields in the original literature procedure were acceptable for the Pictet−Spengler reaction, our yields had decreased to unac-

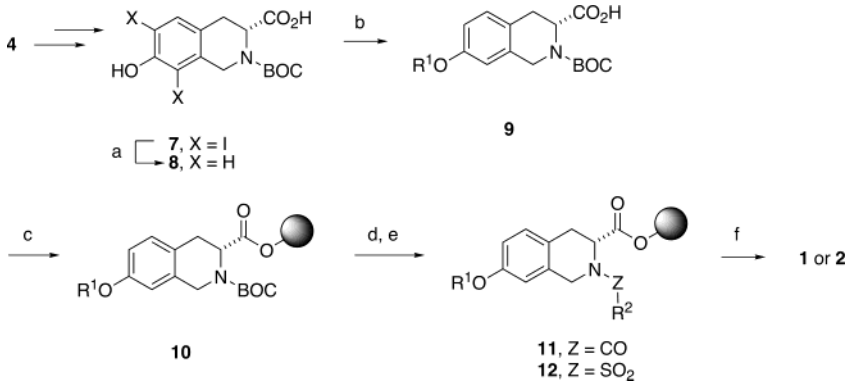
* To whom correspondence should be addressed. Present address: Celera Genomics, 180 Kimball Way, South San Francisco, CA 94080. Tel.: 650-866-6695. Fax: 650-866-6655. E-mail: jeff.dener@celera.com.

10.1021/cc020105t CCC: $27.50
Published on Web 06/19/2004

Scheme 1. General Approach to the Synthesis of Tetrahydroisoquinoline-3-Carboxamides on Solid Support

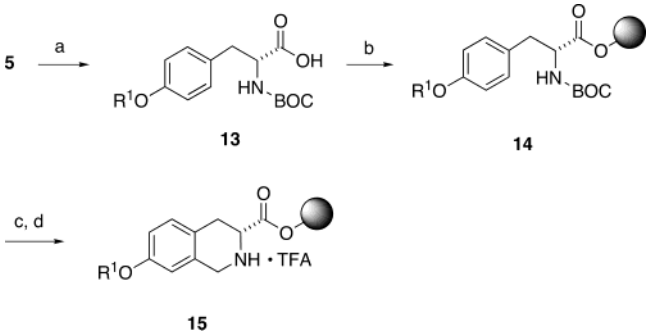


Scheme 2. Solution-Phase Synthesis of Tetrahydroisoquinoline Scaffolds and Subsequent Functionalization on Solid Support[a]



[a] Reagents and conditions: (a) H_2, Pd−C, Et_3N, MeOH, then acid; (b) R^1−hal, KOH, KI, DMSO, 60−70 °C (hal = Br or I); (c) **6**, DIC, 4-DMAP, CH_2Cl_2; (d) TFA; (e) R^2−COCl or R^2−SO_2Cl, NMM; (f) R^3−NH_2, py or 1,4-dioxane.

Scheme 3. Solid-Phase Synthesis of Tetrahydroisoquinolines via a Pictet−Spengler Reaction on Solid Support[a]



[a] Reagents and conditions: (a) R^1−X, KOH, KI, DMSO, 60−70 °C (X = Br or I); (b) **6**, DIC, 4-DMAP, CH_2Cl_2; (c) TFA, CH_2Cl_2; (d) $(CH_2O)_n$, TFA, toluene, 80 °C.

ceptable levels upon scale-up. Furthermore, this route suffered from poor throughput in the reduction of **7** to **8** because of the large volumes of solvent required for the reaction. With these problems in mind, we then evaluated the Pictet−Spengler reaction on carboxyl-supported ethers of *N*-BOC-L-tyrosine (Scheme 3) derived from resin **6**. This approach offered some advantages in addition to avoiding the liabilities to scale-up outlined above. First, only one step was required for large-scale, solution-phase scaffold synthesis, which was conveniently performed on a multigram scale. Second, the site isolation afforded by employing solid-phase chemistry avoids the formation of polymers between the 4-hydroxyphenyl ring of *N*-BOC-L-tyrosine with paraformaldehyde, a side reaction of the Pictet−Spengler reaction known to be responsible for low yields in the solution-phase chemistry.[4,7]

Alkylation of commercially available *N*-BOC-L-tyrosine (**5**) with alkyl and benzyl halides on a 700−900 mmol scale afforded the corresponding tyrosine ethers (**13**) in excellent yields. The structures and yields for each of the ethers prepared according to this route are reported in Table 1. In addition, several tyrosine ethers were commercially available. Attachment of the commercial and synthetic derivatives of **13** to resin **6** was accomplished under conditions similar to those shown in Scheme 2, affording phenyl ester **14**. The key Pictet−Spengler reaction was then performed in a two-step process by first removing the BOC group of **14** with a mixture of TFA, CH_2Cl_2, and anisole (50:48:2) at room temperature and then treating the resulting TFA salt with 600 mol % of paraformaldehyde in 1:1 TFA/toluene at 80 °C to give the tetrahydroisoquinoline **15**. The success of this reaction sequence was determined by the acylation and cleavage process as performed in Scheme 2. The required heating times for each substrate in the Pictet−Spengler reaction were optimized for maximal conversion to product with simultaneous minimization of the relative amount of side products. Decomposition and dealkylation of the ether side chain were common side reactions, and reaction times to suppress the formation of these byproducts had to be determined specifically for each solid-supported ester derivative **14**. Impurities derived from the resulting 7-hydroxy-1,2,3,4-tetrahydroisoquinoline or uncyclized tyrosine derivatives were identified by analysis of the reaction products obtained by sulfonylation and cleavage of the carboxyl-supported Pictet−Spengler intermediate **15** with an amine, typically *n*-butylamine (vide infra; see Scheme 6). In addition, some impurities containing a molecular ion of [M + 104] were observed, which could be best explained as the product derived from a Friedel−Crafts reaction between the solvent, paraformaldehyde, and the aromatic ring of tyrosine. Chart 1 shows a proposed structure obtained after sulfonylation and cleavage from the resin. Proton NMR analysis of a sample of this impurity isolated after HPLC provided evidence for the formation of regioisomers, around

Table 1. Synthetic Tyrosine Ethers (**13**) Prepared According to Scheme 3

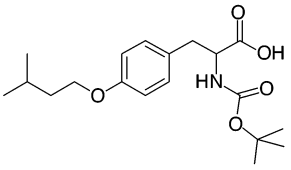
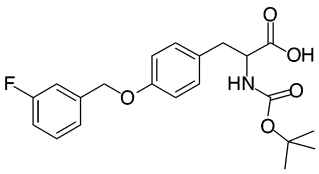
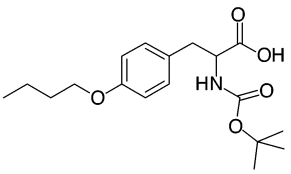
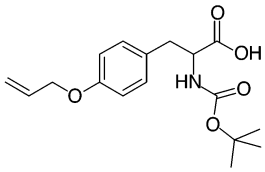
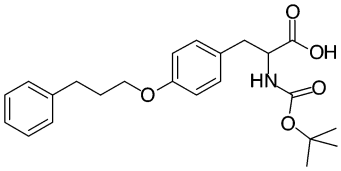
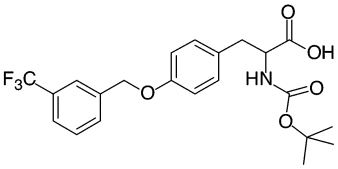
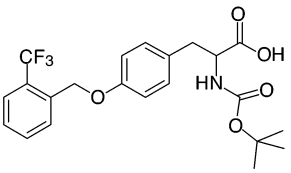
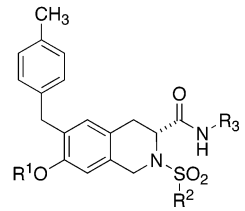
Compound	Structure	Yield (%)
13a		99
13b		99
13c		99
13d		99
13e		99
13f		99
13g		87

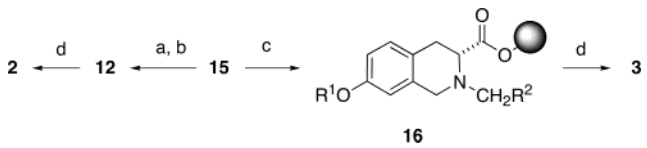
Chart 1. Proposed Solvent−Paraformaldehyde Adduct Believed to Form as an Impurity in the Pictet−Spengler Cyclization[a]



[a] A single regioisomer is shown.

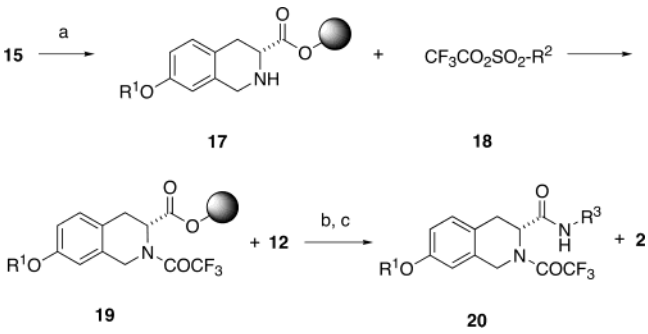
either the toluene ring or the aromatic ring of the tetrahydroisoquinoline nucleus. Although other solvents were explored to suppress this impurity, toluene provided the best results overall, as determined by the minimal formation of this solvent−formaldehyde adduct relative to the formation

Scheme 4. Functionalization and Cleavage of Pictet−Spengler Product from Resin **15**[a]



[a] Reagents and conditions: (a) Et_3N, DMA; (b) R^2-SO_2Cl, Et_3N, DMA; (c) R^2-CHO, py·BH_3, DMA; (d) R^3-NH_2, py, or 1,4-dioxane.

Scheme 5. Formation of the *N*-(Trifluoroacetamido)-tetrahydroisoquinoline Impurity **20**[a]

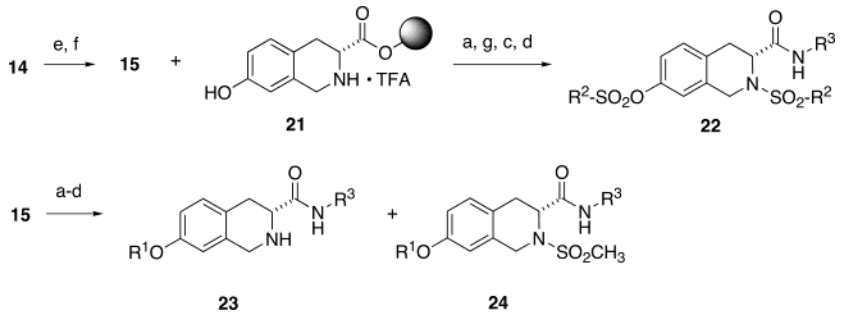


[a] Reagents and conditions: (a) R^2-SO_2Cl, Et_3N; (b) R^3-NH^2, py; (c) amine extraction.

of other impurities. In addition, use of high-dilution conditions in the Pictet−Spengler reaction suppressed formation of the solvent−paraformaldehyde adducts to ≤10% of the product mixture. Once the Pictet−Spengler reaction conditions had been optimized for each tyrosine ether **13**, the subsequent transformations on solid support were performed on a 95−100 mmol scale, employing 80 g of resin **6**.

As shown in Scheme 4, acylation of the support-bound intermediate **15** was performed under conditions similar to those described previously (Scheme 2). However, the use of the TFA salt **15** obtained from the Pictet−Spengler sequence proved to be problematic when sulfonyl chlorides were employed. In this case, use of the TFA salt resulted in the formation of the trifluoroacetamide **20**, along with the sulfonamide **2**. The production of **20** as a contaminant is postulated to arise by the reaction of $CF_3CO_2^-$ in **15** with the sulfonyl chloride to give the mixed anhydride **18**, which subsequently reacts with amine **17** (Scheme 5). Conversion of the amine salt **15** to the free base **17** by treatment of the resin with triethylamine prior to exposure to the sulfonyl chloride and triethylamine avoided the formation of trifluoroacetamide impurity **20**. Another liability in this reaction concerned the structural requirements of the sulfonyl chloride in this transformation. We observed that only aromatic sulfonyl chlorides gave satisfactory results (yield and conversion) in the acylation of resin **15**. When alkyl sulfonyl chlorides, such as methanesulfonyl chloride, were employed in the sulfonylation of resin **15**, substantial amounts of amide **23** was observed along with the desired sulfonamide **24**, indicative of incomplete sulfonylation (Scheme 6). Other impurities observed included the sulfonate ester **22**, which arises from ether cleavage during the Pictet−Spengler reaction followed by reaction of the sulfonyl chloride with both the secondary amine and hydroxyl of support-bound intermediate **21**. Typically, the amounts of impurities derived from **21** were kept to ≤10% after the optimum cyclization

Scheme 6. Impurities and Side Reactions Observed during Reaction Optimization and Building-Block Validation[a]



[a] Reagents and conditions: (a) Et_3N, DMA; (b) CH_3-SO_2Cl, Et_3N; (c) R^3-NH_2, py; (d) amine extraction; (e) TFA, CH_2Cl_2; (f) $(CH_2O)_n$, TFA, toluene, 80 °C; (g) R^2-SO_2Cl, Et_3N.

times had been determined for each solid-supported tyrosine ether **14**. However, some benzylic and allylic ethers of tyrosine were prone to C−O bond cleavage because of their instability to the strongly acidic conditions required for the Pictet−Spengler cyclization reaction. Examples included the tyrosine ethers derived from 4-bromo-2-methylbutene and 3,5-dimethylbenzyl bromide.

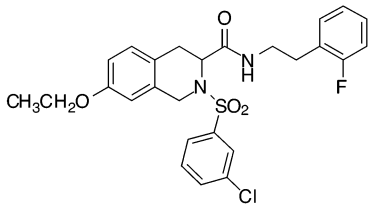
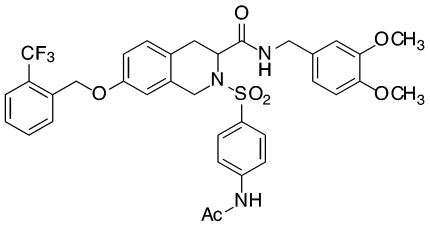
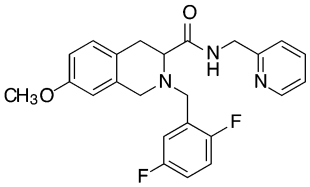
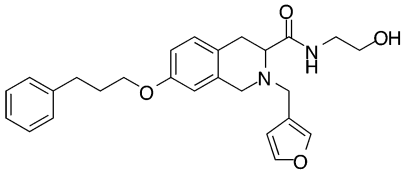
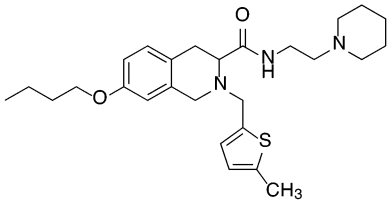
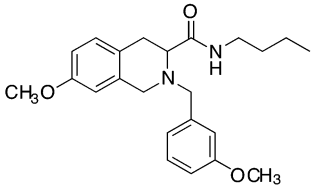
In addition to its reaction with sulfonyl chlorides, support-bound amine **15** could be converted to the corresponding tertiary amine **16** via reductive amination with aldehydes (Scheme 4). Several reducing agents were successful in cleanly promoting this transformation, specifically pyridine−borane complex and sodium triacetoxyborohydride. Being a liquid, the former reagent was generally preferred for high-throughput synthesis for ease of handling relative to the solid reducing reagent $NaBH(OAc)_3$. Optimization of the reaction conditions indicated that 500−1000 mol % of the reducing reagent and 450−500 mol % of aldehyde were required for satisfactory conversion to **16**. Other reducing agents, such as *N*,*N*-diisopropylethylamine−borane and *N*-ethylmorpholine−borane, were inferior to both pyridine−borane and triacetoxyborohydride, typically resulting in incomplete conversion of **15** to tertiary amine **16** under similar reaction conditions.

We observed that the TFA salt of the amine was essential for successful reductive amination to the tertiary amine **16**. Furthermore, either aliphatic or aromatic aldehydes could be successfully used in this transformation (Scheme 4). Both *N*,*N*-dimethylacetamide and chloroform could be employed as the solvent for the reductive amination reactions. However, *N*,*N*-dimethylacetamide was preferred in the application of this chemistry to high-throughput organic synthesis because this solvent was less prone to evaporation, making it better suited for use in open reaction vessels (e.g., 96-well plates). Use of *N*,*N*-dimethylacetamide as the solvent in such vessels avoided resin losses due to the combination of hydrogen gas liberated during the reductive amination reaction and the tendency of the resin to float near the surface in solvents such as chloroform.

Reaction of the support-bound ester with amines afforded the desired amides **1**−**3** upon cleavage from the resin. In general, secondary amines reacted much more slowly than primary amines with the exception of cyclic amines such as derivatives of piperazine and piperidine. Furthermore, primary amines with branching at the α-carbon gave products in lower yields and purities upon exposure to either resin **12** or resin **16**. Removal of the excess amine was conveniently performed using a solid-supported liquid−liquid extraction (SLE) protocol employing diatomaceous earth as the support and aqueous acid as the aqueous buffer.[9] For products derived from the reductive amination sequence, water-soluble amines were used to obtain the desired products. Removal of excess amine could then be performed with pure water as the aqueous buffer, avoiding the potential for product losses due to the protonation and subsequent extraction of the basic tertiary amine **3** into an acidic aqueous buffer in the SLE step.

Table 2 shows examples of tetrahydroisoquinoline derivatives produced according to Scheme 4. The yield and purity data are for crude material that was analyzed using a weight-percent purity method described previously.[10] The Experimental Section contains analytical data (NMR and combustion analyses) generated for these compounds after purification by reverse-phase HPLC. In some cases, yields were low as a result of losses on transfer of solutions, especially during the amine extraction (SLE) process. Furthermore, during development of the support-bound Pictet−Spengler route, we noted that certain solvents were not suitable for washing the resin because of premature cleavage of the support-bound ester derivatives from the resin. In particular, exposure of resin **15** or **17** (R^1 = 3-methylbutyl, derived from **13a**) to methanol for 45 min generated up to 30−35% of the methyl ester, occasionally contaminated with the corresponding acid. However, the nature of the intermediate on the support determined the potential for premature hydrolysis by the wash solvents, as indicated by the data reported in Table 3. For example, resin-bound intermediates **12** and **16** (entries 1 and 2) were not prone to hydrolysis under these conditions, indicating that the sulfonylated or tertiary amine derivatives of tetrahydroisoquinoline are stable as support-bound esters on Marshall resin. Furthermore, support-bound BOC-tyrosine ester **14** afforded similar results, also supporting the fact that the substitution of the nitrogen is crucial to the stability of the resin to potential nucleophilic cleavage. In contrast, the secondary amine **17** or its TFA salt **15** (entries 3 and 4) are much more prone to methanolysis from the resin under these conditions. Therefore, these resins require careful handling and storage to minimize losses due to premature hydrolysis of the support-bound intermediates. Our optimized protocol for the synthesis of these carboxyl-supported tyrosine- and tetrahydroisoquinoline ethers does not require the use of methanol or similar hydrolytic solvents.

Table 2. Structures and Purities of Compounds Prepared According to Scheme 4

Compound	Structure	Yield (%)[a]	Purity (%)[b]
2a		29	66
2b		33	50
3a		52	99
3b		57	71
3c		49	81
3d		49	74

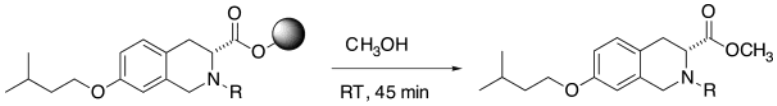
[a] Yield of crude material. [b] By quantitation against purified and fully characterized samples; see text for details.

In summary, we have shown that a Pictet−Spengler reaction can be performed on carboxyl-support tyrosine ethers attached to a nucleophile-cleavable resin. The resulting products are valuable precursors to 1,2,3,4-tetrahydroisoquinoline derivatives containing three sites of diversity. This approach offers an advantage to the strategy of large-scale solution-phase synthesis of a tetrahydroisoquinoline scaffold, followed by attachment to the resin. The solid-phase Pictet−Spengler reaction and subsequent reactions on the support further expand the versatility of resin **6**, which has already proven to be extremely valuable to the solid-phase synthesis of other heterocyclic molecules.

Experimental Section

General. Proton and carbon-13 NMR spectra were recorded using a JEOL Eclipse FT-NMR spectrometer at 270 and 67.5 MHz, respectively. Alternatively, carbon-13 spectra were also obtained on a General Electric QE-300 FT-NMR spectrometer at 75 MHz. Elemental analyses were performed by Robertson Microlit Laboratories Inc., Madison, NJ. MS and LC-MS results were obtained from either a Perkin-Elmer Sciex API150 spectrometer, interfaced with a Hewlett-Packard HP1100 HPLC, or a Finnigan TSQ7000 instrument connected to a Hewlett-Packard HP1090 HPLC.

Table 3. Effect of Nitrogen Substitution on Methanolysis of Support-Bound Tetrahydroisoquinoline Esters



entry	R	mass recovered (mg)[a]	comments
1	$SO_2C_6H_4CH_3$	≤1	
2	$CH_2C_6H_5$	≤1	
3	H	45	
4	H	40	TFA salt

[a] A sample of each resin (500 mg) was exposed to methanol (2 mL) for 45 min, and then the methanol solution was collected and evaporated to give the amounts shown in the table. Products were characterized by LC-MS and ^{1}H NMR analyses.

Three BOC-tyrosine derivatives were purchased from commercial sources: BOC-*O*-methyl-L-tyrosine, BOC-*O*-ethyl-L-tyrosine, and BOC-*O*-(2,6-dichlorobenzyl)-L-tyrosine. The remaining seven were prepared by alkylation of BOC-L-tyrosine with commercially available alkyl bromides. Marshall resin [(4-hydroxyphenyl)thiomethylpolystyrene, **6**] was obtained from Midwest Biotech (loading = 1.2 mmol/g). Sulfonyl chlorides, amines, solvents, and reagents were obtained from commercial sources and used as received.

Representative Procedure for Alkylation of BOC-L-tyrosine: *N*-α-*t*-BOC-*O*-(3-methylbutyl)-L-tyrosine (13a). A solution of BOC-L-tyrosine (200 g, 710 mmol) in DMSO (1000 mL) was cooled in an ice bath. To this solution was added over 30 min a cooled solution of 3.4 M aqueous KOH prepared from 85% KOH (114.8 g, 1700 mmol) and water (500 mL). The solution was then removed from the ice bath and treated with potassium iodide (18.28 g, 120 mmol) followed by 1-bromo-3-methylbutane (132.8 g, 890 mmol, 105.4 mL). The solution was then heated to 60−65 °C for 15−18 h. The reaction progress was monitored by HPLC-UV and LC-MS, and an additional portion of each 1-bromo-3-methylbutane (27.2 g, 180 mmol, 21.6 mL) and KOH (6.6 g, 118 mmol) was added after 3 h at 60−65 °C to drive the reaction to completion. After an additional 13 h of heating, no starting material remained. The reaction mixture was cooled to room temperature, diluted with water (1000 mL), and washed with diethyl ether (2 × 1000 mL). The aqueous layer was then acidified to pH 2−3 with 85% phosphoric acid (100 mL), and the oily mixture was extracted with ethyl acetate (1 × 2000 mL). The combined organic extracts were washed with water (500 mL) and saturated aqueous sodium chloride (1 × 750 mL), dried with sodium sulfate, and concentrated in vacuo to give 249 g (99%) of *N*-α-*t*-BOC-*O*-(3-methylbutyl)-L-tyrosine (**13a**) as a viscous yellow oil. ^{1}H NMR (270 MHz, DMSO-d_6) δ 7.12 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 4.05−3.90 (m with t at 3.93, J = 6.7 Hz, 3H), 3.32 (s, 3H), 2.92 (dd, J = 13.6, 4.7 Hz, 1H), 2.72 (dd, J = 13.6, 10.4 Hz, 1H), 1.84−1.69 (m, 1H), 1.57 (q, J = 6.4 Hz, 2H), 1.32 (s, 9H), 0.90−0.93 (d, J = 6.4 Hz, 6H); ^{13}C NMR (DMSO-d_6, 67.5 MHz) δ 174.2, 157.8, 156.0, 130.6, 130.3, 114.7, 78.6, 66.3, 56.0, 38.0, 36.2, 28.7, 25.1, 23.0; MS (ESI) m/z 352.2 [(M + H)$^+$].

Other derivatives of **13a** were prepared in >85% yields under similar conditions, as reported below and in Table 1.

***N*-α-*t*-BOC-*O*-(3-fluorobenzyl)-L-tyrosine (13b).** According to the general procedure, 3-fluorobenzyl bromide (166.4 g, 890 mmol) was reacted with BOC-L-tyrosine (200 g, 710 mmol), potassium iodide (18.28 g, 120 mmol), and 3.4 M aqueous KOH (500 mL), followed by a second addition of the alkyl halide (34 g, 180 mmol) and KOH (6.6 g, 118 mmol), to give 276 g (99%) of **13b** as a viscous yellow oil. ^{1}H NMR (270 MHz, DMSO-d_6) δ 7.47−7.39 (m, 1H), 7.29−7.22 (m, 2H), 7.16 (d, J = 8.41 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H) 4.07−3.98 (m, 1H), 2.95 (dd, J = 14.4, 5.2 Hz, 1H), 2.74 (dd, J = 13.9, 10.4 Hz, 1H) 1.31 (s, 9H); ^{13}C NMR (67.5 MHz, DMSO-d_6) δ 174.2, 157.3, 156.0, 140.9, 140.7, 130.9, 130.7, 124.0, 114.9, 114.5, 78.6, 68.8, 55.9, 36.2, 28.7; MS (ESI) m/z 390.2 [(M + H)$^+$].

***N*-α-*t*-BOC-*O*-butyl-L-tyrosine (13c).** According to the general procedure, iodobutane (100 mL, 162 g, 890 mmol) was reacted with BOC-L-tyrosine (200 g, 710 mmol) and 3.4 M aqueous KOH (500 mL), followed by a second addition of alkyl halide (20.4 mL, 180 mmol) and KOH (6.6 g, 118 mmol), to give 240 g (99%) of tyrosine ether **13c** as a viscous yellow oil that solidified on standing. ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.58 (br s, 1H), 7.08 (d, J = 7.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 5.02 (d, J = 7.9 Hz, 1H), 4.62−4.51 (m, 1H), 4.39−4.28 (br s, 1H), 3.93 (t, J = 6.4 Hz, 2H), 3.16−2.78 (m, 3H), 1.80−1.68 (m, 2H), 1.55−1.40 (m, 10H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 176.4, 158.2, 156.4, 155.4, 130.3, 127.5, 114.5, 80.1, 67.6, 54.4, 36.9, 31.3, 28.2, 19.2, 13.8; MS (ESI) m/z 338.3 [(M + H)$^+$].

***N*-α-*t*-BOC-*O*-(prop-2-enyl)-L-tyrosine (13d).** According to the general procedure, allyl bromide (78.8 mL, 107 g, 890 mmol) was reacted with BOC-L-tyrosine (200 g, 710 mmol), KI (18.28 g, 120 mmol), and 3.4 M aqueous KOH (500 mL), followed by a second addition of alkyl halide (15.6 mL, 180 mmol) and KOH (6.6 g, 118 mmol), to give 228 g (99%) of **13d** as a viscous tan oil that solidified on standing. ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.28 (br s, 1H), 7.09 (d, J = 8.2 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 6.11−5.97 (m, 1H), 5.42 (dd, J = 17.3, 1.5 Hz, 1H), 5.28 (dd, J = 10.4, 1.2 Hz, 1H), 4.98 (d, J = 7.9 Hz, 1H), 4.62−4.35 (m with d at 4.51, J = 5.4 Hz, 3H), 3.15−2.75 (m, 2H), 1.55−1.25 (m, 9H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 176.4, 157.7, 155.4, 133.2, 130.4, 127.9, 117.6, 114.8, 80.2, 86.8, 54.3, 36.9, 28.3; MS (ESI) m/z 322.0 [(M + H)$^+$].

***N*-α-*t*-BOC-*O*-(3-phenylpropyl)-L-tyrosine (13e).** According to the general procedure, 1-bromo-3-phenylpropane (134 mL, 175 g, 890 mmol) was reacted with BOC-L-tyrosine (200 g, 710 mmol), potassium iodide (18.28 g, 120 mmol),

and 3.4 M aqueous KOH (500 mL), followed by a second addition of alkyl halide (27.2 mL, 180 mmol) and KOH (6.6 g, 118 mmol), to give 284 g (99%) of tyrosine ether **13e** as an off-white solid. ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.61 (br s, 1H), 7.34−7.14 (m, 5H), 7.08 (d, J = 7.9 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 4.98 (d, J = 7.9 Hz, 1H), 4.62−4.52 (m, 1H), 3.92 (t, J = 6.4 Hz, 2H), 3.17−2.94 (m, 2H), 2.79 (t, J = 7.2 Hz, 2H), 2.17−2.02 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 158.1, 155.4, 141.5, 130.4, 128.5, 128.4, 127.7, 125.9, 114.6, 80.2, 66.9, 54.4, 36.9, 32.1, 30.8, 28.3; MS (ESI) m/z 400.0 [$(M + H)^+$].

***N*-α-*t*-BOC-*O*-3-(trifluoromethylbenzyl)-L-tyrosine (13f).** According to the general procedure, 3-(trifluoromethyl)-benzyl bromide (210 g, 890 mmol) was reacted with BOC-L-tyrosine (200 g, 710 mmol), KI (18.28 g, 120 mmol), and 3.4 M aqueous KOH (500 mL), followed by a second addition of the alkyl halide (43 g, 180 mmol), KI (18.28 g, 120 mmol), and KOH (6.6 g, 118 mmol), to give 312 g (99%) of **13f** as a viscous yellow oil that solidified on standing. ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.64 (br s, 1H), 7.68 (s, 1H), 7.58 (t, J = 5.9 Hz, 2H), 7.49 (d, J = 7.7 Hz, 1H), 7.12 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 6.48 (br d, J = 6.7 Hz, 1H), 4.59 (br q, J = 6.9 Hz, 1H), 3.17−2.83 (m, 3H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 157.4, 155.4, 138.0, 130,5, 128.9, 128.7, 124.6, 123.9, 122.2, 114.8, 81.6, 80.2, 69.1, 56.2, 54.4, 36.9, 28.1; MS (ESI) m/z 439.8 [$(M + H)^+$].

***N*-α-*t*-BOC-*O*-2-(trifluoromethylbenzyl)-L-tyrosine (13g).** According to the general procedure, 2-(trifluoromethyl)-benzyl bromide (210 g, 890 mmol) was reacted with BOC-L-tyrosine (200 g, 710 mmol), potassium iodide (18.28 g, 120 mmol), and 3.4 M aqueous KOH (500 mL), followed by a second addition of the alkyl halide (43 g, 180 mmol) and KOH (6.6 g, 118 mmol), to give 270 g (87%) of tyrosine ether **13g** as a flaky, white, sticky solid. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.68 (dd, J = 16.1, 7.8 Hz, 2H), 7.50 (t, J = 7.4 Hz, 1H), 7.36 (t, J = 7.4 Hz, 1H), 7.18−7.08 (m, 2H), 6.89 (d, J = 8.4 Hz, 2H), 5.25−5.10 (m with s at 5.21, 3H), 4.61 (br q, J = 6.9 Hz, 1H), 4.44−4.30 (m, 1H), 3.04 (dd, J = 13.6, 5.9 Hz, 1H), 2.90−2.82 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 157.4, 155.4, 135.6, 132.0, 130.5, 128.6, 127.6, 125.8, 122.5, 114.9, 80.2, 66.1, 54.3, 37.0, 28.2; MS (ESI) m/z 440.2 [$(M + H)^+$].

Preparation of Resin 14. The *O*-alkyl-*N*-BOC-tyrosine derivative (**13**; 288 mmol) was dissolved in dichloromethane (750 mL) and cooled in an ice bath. With stirring, the solution was treated for 1−2 min with diisopropylcarbodiimide (DIC; 45.0 mL, 36.3 g, 288 mmol), and a precipitate formed. The mixture was stirred for an additional 10 min and removed from the ice bath. During this time, a 2-L Nalgene bottle was charged with Marshall resin **6** (80 g, 96 mmol) and dichloromethane (250 mL). To the BOC-tyrosine derivative/DIC solution was added a solution of dimethylaminopyridine (DMAP; 3.51 g, 28.8 mmol) in dichloromethane (100 mL). The resulting solution was quickly added to the resin, and the bottle was capped and shaken manually for 5−10 min, with occassional venting. The bottle was then tightly capped and shaken on a platform shaker for 18−24 h. After this time, the slurry was filtered with a glass-fritted funnel using additional dichloromethane (100 mL) to rinse the resin from the bottle. The resin was washed with dichloromethane (2 × 1000 mL) and then alternate portions of diethyl ether (3 × 500 mL) and dichloromethane (3 × 1000 mL), followed by a final rinse with diethyl ether (2 × 500 mL). The resin was dried by suction under nitrogen and then transferred to a 500-mL wide-mouthed Nalgene bottle and dried under vacuum overnight. Each resin was analyzed by the $FeCl_3$/pyridine test (see below) to determine the completeness of the acylation reaction.

$FeCl_3$/Pyridine Test for Free Phenol.[6b] A small amount of each resin was placed in a test tube and treated with dichloromethane (5 drops), pyridine (5 drops), and a 0.5 M solution of $FeCl_3$ in chloroform (5 drops). After a 5−10-min reaction period, the resin was filtered, washed with 2−3 portions of dichloromethane, and then visually inspected. A purple-gray color indicated that substantial free phenol was present. If no color change was observed, coupling was complete.

Support-Bound Pictet−Spengler Reaction. Preparation of Resin 15. A 2-L Nalgene bottle was charged with resin and dichloromethane (250 mL). To this slurry was added a 50:48:2 solution of TFA/dichloromethane/anisole (800 mL). The bottle was capped loosely and shaken vertically on a platform shaker for 1.5 h. The slurry was filtered with a glass-fritted funnel using additional dichloromethane (100 mL) to rinse the resin from the bottle. The resin was washed with dichloromethane (5 × 1000 mL) and then alternate portions of diethyl ether (3 × 500 mL) and dichloromethane (3 × 1000 mL), followed by a final rinse with diethyl ether (2 × 500 mL). The resin was dried by suction under nitrogen, transferred to a 500-mL Nalgene bottle, and dried under vacuum.

Paraformaldehyde (17.4 g, 576 mmol, 600 mol %) was dissolved in TFA (1440 mL) and toluene (1440 mL) and stirred with an overhead mechanical stirrer. The dry resin was added to this solution, which was then heated in a preheated oil bath to 80 °C for 2.5−4 h. The resin was siphoned from the flask into a glass-fritted funnel using vacuum, with dichloromethane being employed to assist in the transfer of residual resin. The resin was then washed with dichloromethane (5 × 1000 mL) and then alternate portions of diethyl ether (3 × 500 mL) and dichloromethane (3 × 1000 mL), followed by a final rinse with diethyl ether (2 × 500 mL). The resin was dried by suction under nitrogen, transferred to a 500-mL Nalgene bottle, and dried under vacuum overnight. The resin was stored in tightly capped Nalgene bottles to minimize exposure to atmospheric moisture.

Preparation of Support-Bound Sulfonamide 12 from Resin 15. Resin **15** (125 mg, ca. 125 μmol) was converted to the free amine according to the following wash sequence: DMA (1 × 1 mL), 20% triethylamine in DMA (2 × 1 mL), dichloromethane (2 × 1 mL). This resin was rinsed with DMA (2 × 1 mL) and then treated with 1 mL (0.53 mmol) of a sulfonyl chloride as a 0.53 M solution in DMA. This was followed by the addition of neat triethylamine (74 μL). The reaction mixture was shaken for 18−24 h on a platform shaker, and then the resin was fitered. The resin

was washed with DMA (2 × 1 mL) and then with alternating portions of MeOH (3 × 1 mL) and dichloromethane (3 × 1 mL).

Cleavage of Sulfonamide 12. Preparation of Tetrahydroisoquinoline 2. Resin **12** (125 mg, ca. 125 μmol) was washed with 1,4-dioxane (2 × 1 mL) and then was treated with an amine (1 mL, 0.40 mmol) as a 0.40 M solution in anhydrous 1,4-dioxane. The resin slurry was then shaken for 18−24 h on a platform shaker. The resin was filtered and washed with anhydrous 1,4-dioxane (2 × 450 μL). The combined filtrate and washes were frozen and lyophilized for a minimum of 18 h.

The residue obtained from lyophilization was dissolved in chloroform (1.10 mL), and the solution was added to a fritted vessel previously packed with Varian Hydromatrix diatomaceous earth and treated with either 500 μL of water or 500 μL of 2 N $KHSO_4$. The choice of extraction solvent depended on the hydrophobicity of the amine employed in the cleavage step. In general, hydrophobic amines were best extracted using the acid buffer. The chloroform solution was collected, and the source vessel was washed with chloroform (2 × 450 μL). The combined organic solutions were concentrated in vacuo to give the crude sulfonamide **2**, which was analyzed according to the weight-percent purity method described previously.[10] Yield and purity data for compounds prepared in this manner are listed in Table 1. Data are reported below for representative examples of **2** prepared as described above, which were used for quantitative purity analysis.

2-(3-Chlorobenzenesulfonyl)-7-ethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid [2-(2-Fluorophenyl)-ethyl]amide (2a). Isolated as a yellow, viscous oil after reverse-phase HPLC; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.66 (t, *J* = 1.98 Hz, 1H), 7.56 (dt, *J* = 7.67, 1.73, 1.24 Hz, 1H), 7.45 (dq, *J* = 8.16, 1.24, 0.99 Hz, 1H), 7.32 (t, *J* = 7.92 Hz, 1H), 7.23−7.13 (m, 1H), 7.06−6.99 (m, 3H), 6.89 (d, *J* = 8.41 Hz, 1H), 6.69−6.62 (m, 2H), 6.53 (d, *J* = 2.47 Hz, 1H), 4.40−4.36 (m, 1H), 4.30 (d, *J* = 6.43 Hz, 2H), 3.99−3.89 (m, 2H), 3.76−3.63 (m, 1H), 3.60−3.32 (m, 2H), 3.04 (dd, *J* = 15.59, 4.95 Hz, 1H), 2.74 (t, *J* = 6.93 Hz, 2H), 2.61 (dd, *J* = 15.59, 6.68 Hz, 1H), 1.38 (t, *J* = 6.93 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 170.0, 157.7, 139.0, 135.4, 133.2, 132.6, 131.2, 130.3, 129.1, 128.4, 127.6, 125.6, 125.4, 124.4, 124.2, 115.5, 115.2, 114.0, 112.2, 63.5, 56.9, 46.4, 39.7, 29.0, 14.8; MS (ESI) *m*/*z* 517.1 [(M + H)$^+$]. Anal. Calcd for $C_{26}H_{26}ClFN_2O_4S$: C, 60.40; H, 5.07; N, 5.42. Found: C, 60.01; H, 5.32; N, 5.15.

2-(4-Acetylaminobenzenesulfonyl)-7-(2-trifluoromethylbenzyloxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid 3,4-Dimethoxybenzylamide (2b). Isolated as a white solid after purification by reverse-phase HPLC. ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.62, (s, 5H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.18 (s, 1H), 6.96 (t, *J* = 5.7 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.68 (dd, *J* = 8.2, 2.2 Hz, 2H), 6.6−6.56.57 (m, 2H), 6.34 (dd, *J* = 8.1, 1.7 Hz, 1H), 5.09 (s, 2H), 4.45−4.36 (m, 2H), 4.30−4.08 (m with t at 4.21, *J* = 5.4 Hz, 3H), 3.70 (s, 6H), 3.07 (dd, *J* = 15.1, 3.2 Hz, 1H), 2.47 (dd, *J* = 15.1, 6.2 Hz, 1H), 2.03 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 170.7, 169.1, 157.3, 149.0, 148.2, 143.1, 135.1, 133.2, 132.1, 130.9, 130.1, 129.1, 128.7, 128.6, 127.9, 126.0, 125.9, 125.4, 119.3, 119.1, 114.3, 112.7, 111.1, 110.4, 66.2, 57.2, 55.8, 46.4, 43.1, 29.7, 24.4; MS (ESI) *m*/*z* 698.3 [(M + H)$^+$]. Anal. Calcd for $C_{35}H_{34}F_3N_3O_7S \cdot 1/2H_2O$: C, 59.48; H, 4.99; N, 5.95. Found: C, 59.55; H, 4.75; N, 5.60.

Reductive Amination of Support-Bound Amine 15. Formation of Support-Bound Tertiary Amine 16. Resin **15** (130 mg, ca. 130 μmol) was rinsed with DMA (2 × 1 mL) and then treated with an aldehyde (1 mL, 0.63 mmol) as a 0.63 M solution in DMA, followed by the addition of borane−pyridine complex (78 μL). The reaction mixture was shaken for 18−24 h on a platform shaker. After this time, the solvents were drained, and the resin was washed with DMA (2 × 1 mL) and then with alternating portions of MeOH (3 × 1 mL) and dichloromethane (3 × 1 mL). This resin was carried on to the next step.

Tetrahydroisoquinoline 3. Resin **16** was washed with anhydrous pyridine (2 × 1 mL) and then treated with an amine (1 mL, 0.50 mmol) as a 0.50 M solution in anhydrous pyridine. The resin slurry was shaken for 40−48 h on a platform shaker, after which it was filtered. The resin was washed with anhydrous pyridine (2 × 450 μL), and the washes were combined with the original filtrate. The combined filtrate and washes were concentrated in vacuo. The residue was dissolved in chloroform (1.20 mL) and transferred to a fritted syringe cartridge, previously loaded with Varian Hydromatrix diatomaceous earth and treated with H_2O (500 μL). The solution was allowed to percolate through the diatomaceous earth, and the filtrate was collected. The source vessel was rinsed with $CHCl_3$ (2 × 450 μL), and the rinse solution was transferred to the syringe cartridge containing the diatomaceous earth. The resulting filtrate was collected, and the combined chloroform solutions were evaporated; then, the residue corresponding to tetrahydroisoquinoline **3** was dried under high vacuum. Yield and purity data for compounds prepared in this manner are given in Table 1. Data for the purified material prepared according to this procedure are reported below.

2-(2,5-Difluorobenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (Pyridin-2-ylmethyl)amide (3a). Isolated as a beige solid after preparative reverse-phase HPLC, partitioning of the TFA salt between aqueous sodium hydrogen carbonate and chloroform, separation, and evaporation of the organic phase. The residue was then purified by normal-phase HPLC on silica gel using a gradient of methanol/dichloromethane/hexane. ^{1}H NMR (270 MHz, CD_2Cl_2) δ 8.43−8.41 (m, 1 H), 8.12 (br s, 1H), 7.61−7.53 (m, 1H), 7.43−7.35 (m, 1H), 7.18−6.93 (m, 6H), 6.78−6.72 (m, 1H), 6.57 (d, *J* = 1.2 Hz, 1H), 4.41 (t, *J* = 5.4 Hz, 2H), 3.84−3.78 (m, 2H), 3.72 (s, 3H), 3.65−3.57 (m, 2H), 2.99 (d, *J* = 6.7 Hz, 2H); ^{13}C NMR (67.5 MHz, CD_2Cl_2) δ 172.7, 158.6, 157.4, 149.3, 136.9, 135.9, 129.5, 126.5, 122.5, 121.7, 117.9, 116.9, 116.8, 115.8, 115.7, 115.5, 113.0, 112.1, 63.0, 55.5, 52.0, 51.1, 44.5, 27.4; MS (ESI) *m*/*z* 424.3 [(M + H)$^+$]. Anal. Calcd for $C_{24}H_{23}N_2F_2O_2$: C, 68.07; H, 5.47; N, 9.92. Found: C, 67.87; H, 5.29; N, 9.95.

2-Furan-3-yl Methyl-7-(3-phenylpropoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (2-Hydroxyethyl)-

amide (3b). Isolated as a beige solid after reverse-phase HPLC. ^{1}H NMR (270 MHz, CD_2Cl_2) δ 7.61 (br s, 1H), 7.42 (t, J = 1.7 Hz, 1H), 7.37−7.36 (m, 1H), 7.30−7.15 (m, 5H), 7.05 (d, J = 8.4 Hz, 1H), 6.72 (dd, J = 2.5, 4.1 Hz, 1H), 6.59 (d, J = 2.7 Hz, 1H), 3.90 (t, J = 6.4 Hz, 2H), 3.74 (q, J = 15.1, 23.8 Hz, 2H), 3.63 (s, 1H), 3.57−3.53 (m, 4H), 3.48 (t, J = 6.4 Hz, 1H), 3.33−3.26 (m, 2H), 2.97 (d, J = 6.4 Hz, 2H), 2.77 (t, J = 7.2 Hz, 2H), 2.10−2.00 (m, 2H); ^{13}C NMR (67.5 MHz, CD_2Cl_2) δ 174.4, 158.0, 143.8, 142.1, 141.4, 136.2, 129.2, 128.8, 128.7, 126.5, 126.2, 122.4, 113.5, 112.7, 111.3, 67.4, 62.8, 62.1, 54.6, 54.2, 53.8, 53.4, 53.0, 51.7, 49.0, 42.6, 32.4, 31.3, 27.4; MS (ESI) m/z 435.5 [(M + H)$^+$]. Anal. Calcd for $C_{26}H_{30}N_2O_4$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.49; H, 6.71; N, 6.34.

7-Butoxy-2-(5-methylthiophen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (2-Piperidin-1-yl-ethyl)amide (3c). Isolated as a yellow oil after reverse-phase HPLC. ^{1}H NMR (270 MHz, CD_2Cl_2) δ 7.52 (br t, J = 4.7 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.72−6.68 (m, 2H), 6.58−6.53 (m, 2H), 3.88 (t, J = 6.5 Hz, 2H), 3.78 (s, 2H), 3.77 (q, J = 15.6, 28.7 Hz, 2H), 3.50 (t, J = 6.4 Hz, 1H), 3.25 (dddd, J = 6.0, 6.0, 11.9, 11.9 Hz, 2H), 2.97 (d, J = 5.6 Hz, 2H), 2.44 (s, 3H), 2.37−2.25 (m, 5H), 1.76−1.65 (m, 2H), 1.57−1.38 (m, 8H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (67.5 MHz, CD_2Cl_2) δ 172.5, 158.0, 140.8, 139.9, 135.8, 129.5, 126.2, 126.0, 124.8, 113.4, 112.6, 68.0, 61.9, 57.9, 51.3, 36.3, 31.7, 26.5, 26.4, 24.9, 19.6, 15.5, 14.0; MS (ESI) m/z 470.6 [(M + H)$^+$]. Anal. Calcd for $C_{27}H_{39}N_3O_2S$: C, 69.04; H, 8.37; N, 8.95. Found: C, 69.02; H, 8.33; N, 8.83.

7-Methoxy-2-(3-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Butylamide (3d). Isolated as a white wax after chromatographic purification by reverse-phase HPLC. ^{1}H NMR (270 MHz, CD_2Cl_2) δ 7.28−7.15 (m, 2H), 7.06 (d, J = 8.4 Hz, 1H), 6.90−6.78 (m, 3H), 6.72 (dd, J = 2.7, 4.3 Hz, 1H), 6.54 (d, J = 2.4 Hz, 1H), 3.81−3.57 (m, 4H), 3.78 (s, 3H), 3.72 (s, 3H), 3.45 (t, J = 6.4 Hz, 1H), 3.16 (qd, J = 3.0, 9.9 Hz, 2H), 2.99 (d, J = 6.5 Hz, 2H), 1.42−1.32 (m, 2H), 1.27−1.14 (m, 2H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR (67.5 MHz, CD_2Cl_2) δ 172.7, 160.3, 158.5, 140.6, 136.1, 129.8, 129.4, 126.6, 121.3, 114.7, 112.9, 112.0, 62.5, 58.5, 55.5, 51.8, 39.0, 32.2, 27.0, 20.4, 13.9; MS (ESI) m/z 383.5 [(M + H)$^+$]. Anal. Calcd for $C_{23}H_{30}N_2O_3$: C, 72.22; H, 7.91; N, 7.32. Found: C, 71.99; H, 8.01; N, 7.23.

Acknowledgment. We thank Marc Benz, Mike Stock, Jack Yim, Chayling Hendarto, Yelena Zherbina, and Hao Lin for library production, including large-scale resin preparation. In addition, we thank Aladin Sadoun and Aaron Wolfe for large-scale synthesis of the tyrosine ethers. We also thank Mark Irving, Silvia Sadikin, and Jeff Wheatley for purification of final compounds. Last, we are grateful to Liling Fang, Jianmin Pan, Jason Cournoyer, Mark Pennachio, Diana Liu, and Duayne Tokushige for analytical support. This work is dedicated to the memory of Professor Henry Rapoport, an outstanding chemist and teacher whose many contributions to organic synthesis include solid-phase chemistry, as exemplified by his work with solid-supported esters in the Dieckmann cyclization (Crowley, J. I.; Rapoport, H. J. *Org. Chem.* **1980**, *45*, 3215−3227).

References and Notes

(1) For reviews, see: (a) Bunin, B. A.; Dener, J. M.; Livingston, D. A. Application of Combinatorial and Parallel Synthesis to Medicinal Chemistry. In *Annual Reports in Medicinal Chemistry*; Doherty, A. Ed.; Elsevier: New York, 1999; Vol. 34, Chapter 27, pp 267−286. (b) Andres, C. J.; Denhart, D. J.; Deshpande, M. S.; Gillman, K. W. *Comb. Chem. High Throughput Screening* **1999**, *2*, 191−210.

(2) For reviews of carbon−carbon-forming reactions on the solid phase, see: (a) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549−1581. (b) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **2001**, *101*, 137−202.

(3) (a) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449−472. (b) Loughlin, W. A. *Aust. J. Chem.* **1998**, *51*, 875−893. (c) Corbett, J. W. *Org. Prep. Proc. Int.* **1998**, *30*, 489−550. (d) Franzen, R. G. *J. Comb. Chem.* **2000**, *2*, 195−214.

(4) For reviews and key references on the Pictet−Spengler reaction, see: (a) Whaley, W. M.; Govindchari, T. R. *Org. React.* **1951**, *6*, 151. (b) Bates, H. A.; Bagheri, K.; Vertino, P. M. *J. Org. Chem.* **1986**, *51*, 3061−3063.

(5) For references on the formation of tetrahydroisoquinolines on the solid phase, see: (a) Meutermans, W. D. F.; Alewood, P. F. *Tetrahedron Lett.* **1995**, *36*, 7709−7712. (b) Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 4865−4868. (c) Rölfing, K.; Theil, M.; Künzer, H. *Synlett* **1996**, 1036−1038. (c) Sun, Q.; Kyle, D. J. *Comb. Chem. High Throughput Screening* **2002**, 5, *75*−*81*. For a recent review on the solid-phase synthesis of nitrogen heterocycles including tetrahydroisoquinolines, see: Brase, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem.* **2002**, *10*, 2415−2437.

(6) (a) Breitenbucher, J. G.; Hui, H. C. *Tetrahedron Lett.* **1998**, *39*, 8207−8210. (b) Breitenbucher, J. G.; Johnson, C. R.; Haight, M.; Phelan, J. C. *Tetrahedron Lett.* **1998**, *39*, 1295−1298. (c) Fantauzzi, P. P.; Yager, K. M. *Tetrahedron Lett.* **1998**, *39*, 1291−1294. (d) Boldi, A. M.; Dener, J. M.; Hopkins, T. P. *J. Comb. Chem.* **2001**, *3*, 367−373. For the original references describing the synthesis and use of resin **6**, see: Marshall, D. L.; Liener, I. E. *J. Org. Chem.* **1970**, *35*, 867−868. Flanigan, E.; Marshall, G. R. *Tetrahedron Lett.* **1970**, 2403−2406.

(7) Verschueren, K.; Toth, G.; Tourwé, D.; Lebl, M.; Van Binst, G.; Hruby, V. *Synthesis* **1992**, 458−460.

(8) Chung, J. Y. L.; Zhao, D.; Hughes, D. L.; Grabowski, E. J. J. *Tetrahedron* **1993**, *49*, 5767−5776.

(9) Johnson, C. R.; Zhang, B.; Fantauzzi, P.; Hocker, M.; Yager, K. M. *Tetrahedron* **1998**, *54*, 4097−4106. Breitenbucher, J. G.; Arienti, K. L. McClure, K. J. *J. Comb. Chem.* **2001**, *3*, 528−533

(10) Fang, L.; Pan, J.; Yan, B. *Biotechnol. Bioeng.* **2000**, *71*, 162−171.

CC020105T