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Pictet-Spengler Reaction on Solid Support: Synthesis of 1,2,3,4-Tetrahydro-β-Carboline Libraries

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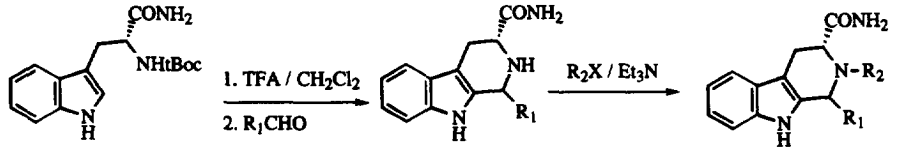
Abstract: The Pictet-Spengler cyclization utilizing tryptophan linked to the Kaiser oxime resin and aldehydes affords the 1,2,3,4-tetrahydro-β-carboline derivatives **6** which can be further functionalized by reaction with acylating reagents. Nucleophilic cleavage with amines affords the final products **7** in high yield and purity. Copyright © 1996 Elsevier Science Ltd

Combinatorial chemistry is a rapidly growing methodology designed to address the two intrinsic challenges of drug discovery i.e. lead identification and lead optimization.[1] Synthesis of a large number of structurally diverse compounds based on known pharmacophores can complement traditional compound libraries derived from natural products and archived chemical collections. Knowledge of lead structures from screening of libraries against target biological assays can be used for the design of focused libraries and accelerate the lead optimization process.

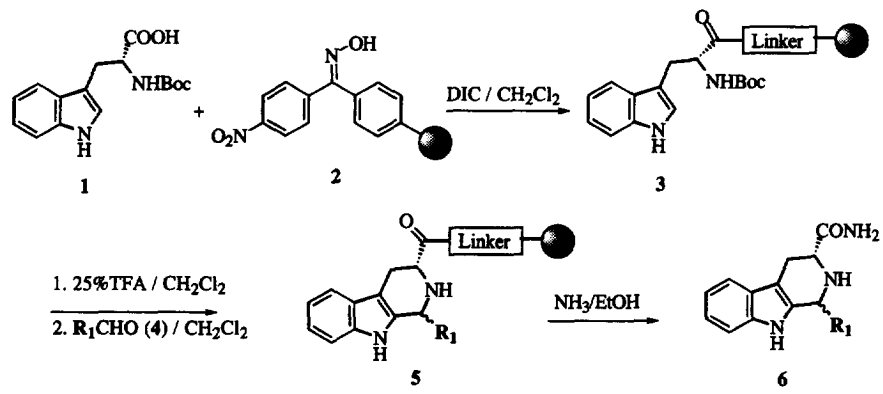
Our interest in utilizing combinatorial chemistry to enrich our compound collection focused on the chemistry of 1,2,3,4-tetrahydropyrido[3,4-*b*]indoles (1,2,3,4-tetrahydro-β-carbolines, THBCs). THBCs as pharmacophores have exhibited a wide range of pharmacological properties. They have been shown to inhibit monoamine oxidase A and bind with nanomolar affinity to serotonin receptors.[2] THBCs also bind to the $GABA_A$ receptor ion channel and modulate molecular mechanisms controlling anxiety, convulsions and sleep.[3] As combinatorial chemistry targets, β-carbolines are useful structures as they possess multiple sites for functionalization allowing the generation of a large number of structurally diverse compounds.

Our approach towards the β-carboline analogs was based on chemistry of the Pictet-Spengler reaction which has been used for the synthesis of both indole and isoquinoline alkaloids.[4] This reaction utilizes tryptophan analogs and aldehydes to afford β-carbolines derivatives that can be further functionalized by reaction with acid halides, isocyanates and sulfonyl chlorides (R_2X).



In extending this reaction to solid-phase chemistry, our two main challenges were to utilize a linker that would be stable to the acid catalyzed Pictet-Spengler reaction and to demonstrate the feasibility of the carbon-carbon bond forming reaction on the solid support.

As shown in Scheme 1, we chose the Kaiser oxime resin[5] **2** (Novabiochem) as our solid support. Peptide literature has shown that the linker is stable to 25% TFA in CH_2Cl_2 and that the cleavage by amines and other nucleophiles affords the facile release of products. Boc-L-Tryptophan (**1**) was attached to the oxime resin under standard conditions utilizing 1,1-diisopropylcarbodiimide (DIC) to afford the polymer bound material **3**. Removal of the Boc protecting group with TFA followed by the addition of the aldehyde **4** afforded the β-carboline analog **5** attached to the oxime resin. Typically the cyclization reaction is complete within 6 h as followed by reversed phase HPLC. Cleavage of the template from the resin utilizing ammonia in ethanol and evaporation of the volatiles afforded the β-carboline derivatives **6** as a mixture of diastereomeric compounds (Method A).[6] The final products were purified by preparative HPLC (C_{18}, CH_3CN/H_2O) and give satisfactory NMR and LC-MS analysis (Table 1).[7]



Scheme 1

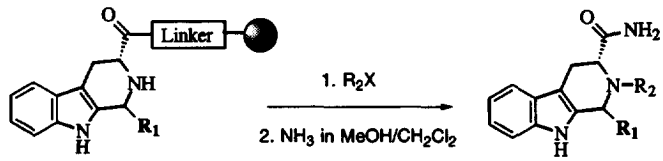
Table 1: β-Carboline Analogs from Pictet-Spengler Reaction on Kaiser Oxime Resin

Compound	R_1	Yield(%)[a,b]
6a	2-methylpropyl	84
6b	phenyl	96
6c	4-chlorophenyl	90
6d	ethyl	94
6e	4-benzyloxyphenyl	91
6f	4-methoxyphenyl	87

[a] Yields determined by preparative HPLC purification. [b] All new compounds were characterized by ^1H NMR spectroscopy

To further functionalize the β-carboline analogs, intermediate **5**, was treated with an acid chloride, isocyanate or sulfonyl chloride (R_2X) for 2 h and cleaved by treatment with ammonia in $MeOH/CH_2Cl_2$

(Scheme 2, Method B[6]). Evaporation of the volatile reagents affords the fully functionalized 1,2,3,4-tetrahydro-β-carboline analogs **7** (Table 2).



Scheme 2

Table 2: Representative β-Carbolines from Matrix Synthesis

Compound	R_1	R_2	Yield (%)[a]
7a	2-methylpropyl	p-toluenesulfonyl	84
7b	2-methylpropyl	dimethylcarbamoyl	89
7c	2-methylpropyl	2-chloroethylaminocarbonyl	90
7d	phenyl	acetyl	70
7e	phenyl	propionyl	82
7f	4-chlorophenyl	dimethylcarbamoyl	88
7g	4-chlorophenyl	2-chloroethylaminocarbonyl	85
7h	ethyl	propionyl	95
7i	ethyl	p-toluenesulfonyl	95
7j	4-methoxyphenyl	acetyl	71

[a] HPLC yield determined from area of peak corresponding to correct molecular weight by LC ES/MS.[7]

In addition to L-tryptophan, other functionalized tryptophan analogs can be used in the Pictet-Spengler reaction. Furthermore, the resin bound intermediate **5** can be cleaved with a wide variety of amines, including amino acids to maximize the diversity of the libraries.

In summary, we have developed a solid phase synthesis of 1,2,3,4-tetrahydro-β-carboline analogs **7** derived from tryptophan derivatives and commercially available aldehydes and acylating agents. The synthesis is amenable to automation and can provide large libraries of spatially distinct molecules for assay in biological systems.

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6. **Method A.** Oxime resin **2** (Novabiochem, 6.0 g, 0.38 mmol/g) suspended in 50 mL CH_2Cl_2 was shaken for 15 min. Boc-L-Tryptophan (**1**) (1.1 g, 3.5 mmol) was added followed by 1,1-diisopropylcarbodiimide (DIC) (548 µl , 3.5 mmol). The resin was shaken for 16 h, washed with CH_2Cl_2 (3 X 50 mL), isopropanol (3 X 50 mL) and CH_2Cl_2 (3 X 50 mL). The resin was divided as necessary for use in subsequent reactions.
   The oxime resin **3** (0.7 g, 0.38 mmol/g) was washed with methylene chloride (3 X 3 mL). 25% TFA in CH_2Cl_2 (3 mL) was added and the resin shaken for 1 min. The resin was flushed free of the TFA solution (N_2). An additional 3 mL of 25% TFA in CH_2Cl_2 was added and the resin shaken for 30 min. The resin was flushed free of the TFA solution. Fresh TFA (25% solution in CH_2Cl_2, 3 mL) was added followed by the aldehyde **4** (6 mmol, 15 equivalents, 2 M final concentration). The reaction was shaken for 6 h. The resin was then flushed free of the liquids, washed with CH_2Cl_2 (3 X 4 mL) followed by DMF (3 X 4 mL) and CH_2Cl_2 (3 X 4 mL). Cleavage of a resin aliquot (0.5 mL saturated NH_3 in EtOH, 2 min) and HPLC analysis indicated formation of the desired tetrahydro-β-carboline product. The resin was split into 4 portions for subsequent reactions.
   Method B. To the tetrahydro-β-carboline on solid support **5** (175 mg, 0.067 mmol) in CH_2Cl_2 (0.5 mL) was added pyridine (0.20 mL of 1M solution in CH_2Cl_2) followed by the acid chloride or sulfonyl chloride (0.20 mL of 1M solution in CH_2Cl_2). In case of the isocyanate, the pyridine was omitted. The resin was shaken for 2 h, flushed and washed sequentially with CH_2Cl_2, DMF and CH_2Cl_2. The resin was then treated with 2 mL of a 1:1 v/v mixture of CH_2Cl_2 and saturated NH_3 in MeOH for 2 h. The resin was filtered, the filtrate collected and evaporated to afford the 1,2,3,4-tetrahydro-β-carboline **7** as a solid.
7. LC ES/MS was performed on a Sciex API III Plus.

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