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Preparation of pilot library with tetrahydro-β-carboline alkaloid core skeleton using tandem intramolecular Pictet–Spengler cyclization

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Abstract—A solid phase strategy has been developed for the synthesis of tetrahydro-β-carboline alkaloid library. The key transformation is an acid-catalyzed tandem intramolecular Pictet–Spengler cyclization from L-tryptophan which forms acyl iminiums with synchronous cleavage of products from the acid-labile SASRIN™ solid support. A pilot library with two diversity points has been successfully synthesized in high purity to demonstrate this strategy.

1. Introduction

Tetrahydro-β-carboline is often found in complex natural products and is frequently associated with biological activity,[1] such as anti-cancer,[2] anti-inflammatory,[3] anti-HIV,[4] anti-depressant,[5] and for erectile dysfunction.[6] *Rauwolfia* alkaloids are representative natural tetrahydro-β-carboline alkaloids which were extracted from the root of *Rauwolfia serpentina* or *Rauwolfia vomitoria*. Reserpine is the most well known antihypertensive drug, derived from this type of alkaloids, which is included in the 'WHO Model List of Essential Drugs' as an antihypertensive agent. Tadanafil, the drug for erectile dysfunction, is not a natural alkaloid, but it has tetrahydro-β-carboline skeleton originated from a natural amino acid, L-tryptophan (Fig. 1).

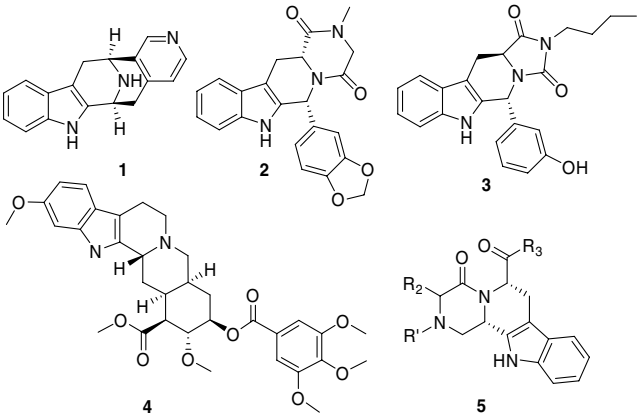

Figure 1. Tetrahydro-β-carboline alkaloids. **1**: Sellowiine; **2**: Tadanafil; **3**: HR22C16; **4**: Reserpine and **5**: designed core skeleton of this study.

The biological importance[7] and therapeutic potentials of tetrahydro-β-carboline alkaloids have stimulated interests in the development of efficient methodology not only in conventional organic synthesis[8] but also in solid-phase combinatorial synthesis.[10] Based on previous reports in the syntheses of tetrahydro-β-carboline ring systems via Pictet–Spengler reaction,[9,10] L-tryptophan, L-tryptophan methyl ester, or its N-substituted derivatives, such as L-abrine methyl ester and *N*-benzyltryptophan methyl ester, were most frequently utilized as a key element with achiral aldehyde in asymmetric intermolecular fashion.[11] There are also a few examples of asymmetric Pictet–Spengler reactions using chiral aldehydes and similar reactions using azalactones as equivalents of arylacetaldehyde.[12]

In this letter, we wish to delineate the efficient synthesis of tetrahydro-β-carboline alkaloids through solid-phase methodology. Tetrahydro-β-carboline alkaloid core skeleton possesses multiple sites for functionalization and permits the generation of a large number of structurally diverse compounds. We especially focused on

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the development of a key transformation, which is an acid-catalyzed tandem intramolecular Pictet–Spengler cyclization from L-tryptophan that forms acyl iminium with synchronous cleavage of substrates from acid-labile solid supports in an asymmetric fashion. In our present investigation, we validated this solid-phase methodology by the successful construction of a pilot library with tetrahydro-β-carboline alkaloid core skeleton using commercially available building blocks such as amino acids and isocyanates.

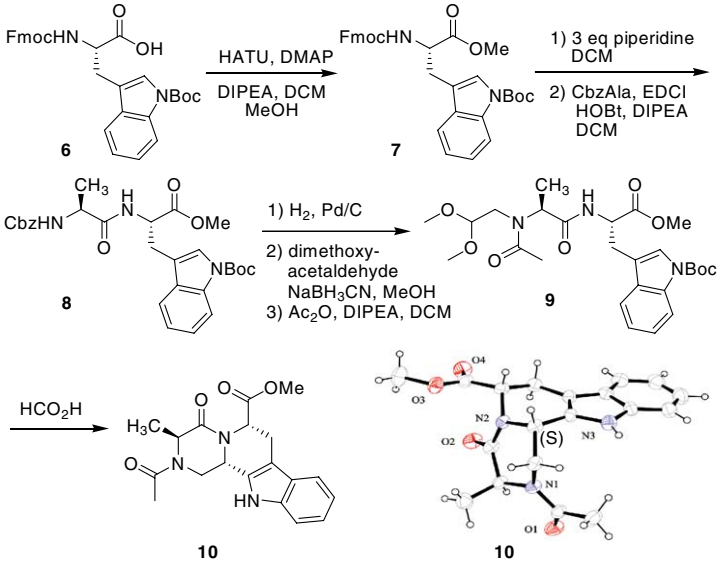
2. Results and discussion

Our synthetic strategy is intramolecular tandem cyclization of active acyl-iminium intermediates with indole moiety from L-tryptophan. As illustrated in Scheme 1, we tried the validation of this route by the synthesis of compound **10** as a representative core skeleton **5** with $R' =$ acetyl, $R_2 =$ methyl, and $R_3 =$ methoxy in solution phase.

The synthesis of representative tetrahydro-β-carboline core skeleton **10** was launched by esterification of FmocTrpOH **6**. The resulting compound **7** was Fmoc-deprotected and converted to secondary amine by reductive amination with dimethoxyacetaldehyde and $NaBH_3CN$. In general, reductive amination with $NaBH_3CN$ is accelerated by small amounts of acetic acid. However, we experienced an additional reductive amination, that is, tertiary amine was a major product, not the desired secondary amine. To control the reactivity of reductive amination, we eliminated acetic acid from reaction condition, which provides the desired secondary amine in 70% yield. The resulting secondary amine was converted to compound **9** by acetylation using a general condition: acetic anhydride and DIPEA in dichloromethane. The final step was the key transformation from linear peptide to cyclic tetrahydro-β-carboline alkaloid. The general condition of a Pictet–Spengler cyclization was under strong acids, such as TFA, toluenesulfonic acid, HCl, and sulfuric acid. In our previous research,[13] we demonstrated an efficient library construction using Pictet–Spengler tandem cyclization with neat formic acid. Here we applied our condition into this synthetic route and obtained the desired compound **10** in high yield (85%). The X-ray crystal structure[14] of compound **10** validated the molecular connectivity as well as the new chiral center (*S* diastereomer) generated by diastereochemically enriched intramolecular Pictet–Spengler cyclization (Scheme 1).[15]

Based on the successful validation of the synthetic strategy in solution phase, we stepped onto the next stage for library construction. We applied the synthetic methodology developed in solution phase into solid-phase synthesis. The key decision to be made was the selection of optimum linker system on solid support. Among acid-labile polymer supports, SASRIN™ resin was selected due to efficient cleavage with neat formic acid. To test this solid support for this synthetic pathway, we attached FmocTrpOH to alcohol moiety on polymer supports through ester linkage. For the direct comparison with solution-phase study, FmocTrp ester on solid support was coupled with L-alanine followed by acetylation with acetic anhydride. The desired compound **10** in free carboxylic acid form was synthesized in excellent purity by acidic cleavage from solid support and simultaneous generation of aldehyde, which leads to acyl-iminium formation and intramolecular Pictet–Spengler tandem cyclization. Treatment with neat formic acid transformed solid-bound liner peptide to complex tetrahydro-β-carboline alkaloids in solution, and the evaporation of formic acid leads to the desired products in high yield and purification without any further purification step, which is essential for the efficiency in library construction.

Due to the limitation of commercially available building blocks in an anhydride form, we transfer amide linkage on R′ to urea functional group by the treatment of secondary amines with isocyanate building blocks. With



Scheme 1. Solution phase validation of designed template and X-ray crystal structure of compound **10**.

this core skeleton **14**, we used R_1 instead of R′ in Scheme 2 for clarity. The test reaction was pursued with benzyl isocyanate and L-leucine using a synthetic procedure shown in Scheme 2. To our pleasant surprise, tetrahydro-β-carboline alkaloid with urea group was synthesized in superior yield and purity. After the feasibility test, we started the construction of a pilot library with tetrahydro-β-carboline alkaloid core skeleton.

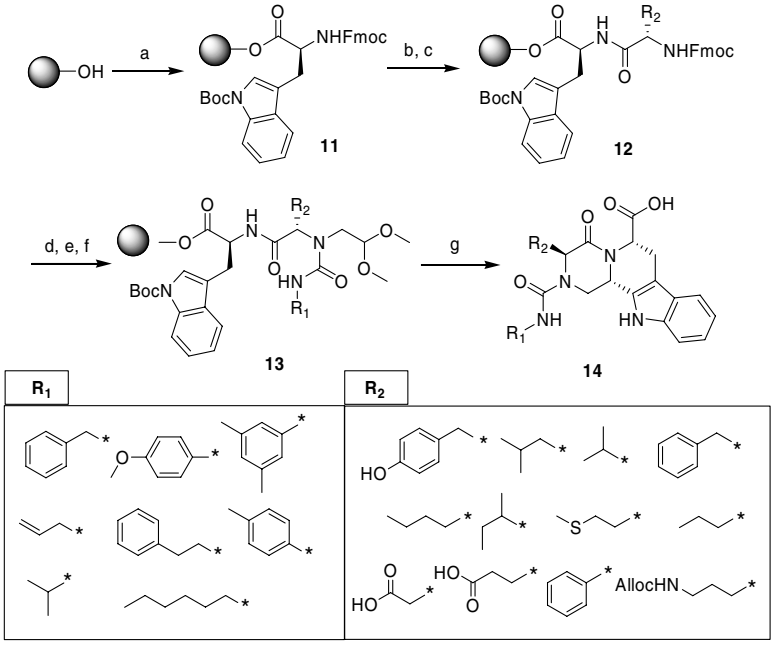
For the construction of a pilot library, we chose R_1 and R_2 as diversity points on tetrahydro-β-carboline alkaloid core skeleton without the realization of R_3 position. The possibility of the diversification on R_3 position was validated by synthesis of representative compound with 4-CF_3OPhNH– as a R_3 group (see Supplementary data). R_1 was diversified by urea formation reaction using 8 commercially available isocyanates. In addition, R_1 can be further diversified with the introduction of *p*-nitrophenyl chloroformate, followed by treatment of various primary amines as an alternative route, which was not pursued for this report. R_2 was introduced by amide coupling of Fmoc protected amino acids, and 12 natural and unnatural amino acids were used in pilot library synthesis (see Scheme 2). With these building blocks, an array of 96 compounds was designed to be synthesized through solid-phase parallel synthesis platform.

The first step for a pilot library construction was the immobilization of L-tryptophan on SASRIN™ resin through ester linkage, which was under the same reaction conditions optimized in solution. Double esterification with 3 equiv of Fmoc–Trp(Boc)–OH provided a sufficient loading (0.65 mmol/g) and unreacted alcohol moieties on solid supports were capped with acetic anhydride/pyridine to ensure the purity of final products in the library. FmocTrp-loaded resins **11** were distributed into the individual deep wells in 96 deep-well filtration blocks, and all syntheses were performed in parallel (see Section 4). Subsequent deprotection of Fmoc group generates the substrate for amide coupling with 12 different Fmoc amino acids, respectively.

After second Fmoc deprotection of dipeptides **12** on solid supports, the reductive amination was performed with above-mentioned conditions. Due to swelling property of solid support, we combined methanol and DMF together in a ratio of 1:1 for reductive amination. The resulting secondary amines were treated with 8 different isocyanates in the presence of DIPEA. The final step was successfully proceeded with neat formic acid at 50 °C through a series of reactions; cleavage, acyl-iminium formation, and intramolecular Pictet–Spengler cyclization. The resulting solution was collected and excess formic acids were evaporated, and subsequent lyophilization with 50% water/acetonitrile yields the desired product as a yellow solid. With these building blocks (see Scheme 2), an array of 96 compounds was synthesized in excellent purities through solid-phase parallel synthesis platform. In Table 1, we randomly selected 11 representative compounds to show the representative purities and yields of a pilot library.

3. Conclusion

In summary, a solid-phase synthetic strategy has been developed for the synthesis of tetrahydro-β-carboline alkaloid library. The key transformation is an intramolecular Pictet–Spengler tandem cyclization on in situ generated acyl-iminium during acidic cleavage from polymer supports. A pilot library with two diversity elements has been synthesized to demonstrate the efficacy



Scheme 2. Solid-phase parallel synthesis of tetrahydro-β-carboline alkaloid library. Reagent and conditions: (a) FmocTrpOH, HATU, DMAP, DIPEA, DMF; (b) 25% piperidine in DMF; (c) Fmoc-protected amino acid, DIC, HOBt, DIPEA, DMF; (d) 25% piperidine in DMF; (e) dimethoxyacetaldehyde, $NaBH_3CN$, MeOH/DMF; (f) R_1NCO, DIPEA, DCE and (g) neat formic acid, 50 °C, 3 h.

Table 1. The purity and yield of representative compounds

Entry	R_1	R_2	Purity[a] (%)	MW	Obsd $[M+H]^+$	Yield[b] (%)
1	$(CH_3)_2CH$	$PhCH_2$	97.8	460.5	461.4	78.6
2	$3,5(CH_3)_2Ph$	$CH_3CH_2CH_2$	85.4	474.6	475.3	85.3
3	*n*-Hexyl	$(CH_3)_2CHCH_2$	97.3	468.6	469.4	79.9
4	CH_2CHCH_2	3-(Alloc)NH-propyl	95.9	509.6	510.4	80.2
5	CH_2CHCH_2	$PhCH_2$	96.4	458.5	459.4	75.3
6	$PhCH_2$	$(CH_3)_2CHCH_2$	82.3	474.6	475.3	90.1
7	$4\text{-}CH_3Ph$	3-(Alloc)NH-propyl	84.8	559.6	560.3	90.5
8	$PhCH_2CH_2$	$CH_3CH_2CH_2$	88.7	474.6	475.3	75.5
9	$PhCH_2CH_2$	$(CH_3)_2CHCH_2$	86.6	488.6	489.5	85.1
10	$4\text{-}CH_3OPh$	$CH_3SCH_2CH_2$	86.3	508.6	509.4	86.3
11	$4\text{-}CH_3OPh$	$(CH_3)_2CH$	83.5	476.5	477.4	75.4

[a] Purity was determined by RP-HPLC/MS analysis of the final crude products after cleavage.
[b] Yield of crude products was determined based on the original loading amount of FmocTrp on the solid supports.

of this strategy. The complete library realization with tetrahydro-β-carboline alkaloid core skeleton is currently underway, which includes the realization of diversity at R_3 position.

4. Experimental

General procedures for the solid phase synthesis of tetrahydro-β-carboline alkaloid library. The reaction steps for the library construction performed in parallel using FlexChem® Synthesis System from SciGene (Sunnyvale, CA) with 96 deep-well filtration blocks.

4.1. FmocTrpOH attachment

2-Methoxy-4-alkoxybenzyl alcohol (SASRIN™) resins (40 mg, 0.93 mmol/g) were swollen in DMF (1.2 mL). A solution of FmocTrp(Boc)OH (3 equiv), HATU [O-(7-azabenotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate] (3 equiv), DMAP (0.1 equiv) and DIPEA (6 equiv) in DMF was added to the resin. After the reaction mixture was shaken for 12 h at room temperature, the resin was washed with DMF, MeOH, and then DCM. All the procedures were repeated twice for optimum loading and acetyl capping was proceeded with acetic anhydride (5 equiv) and pyridine (5 equiv) in dichloroethane for 5 h.

4.2. Fmoc amino acid coupling

To the resin, 25% piperidine in DMF was added and the reaction mixture was shaken for 1 h at room temperature and the resin was washed with DMF, methanol, DCM and then DMF. A solution of Fmoc amino acid (3 equiv), HOBt (3 equiv), DIPEA (6 equiv), and DIC (3 equiv) in DMF was added to the resin after 30 min of acid activation and the reaction mixture was shaken for 12 h at room temperature. The resin was washed with DMF, MeOH, and then DCM.

4.3. Reductive amination

To the resin, 25% piperidine in DMF was added and the reaction mixture was shaken for 1 h at room temperature and the resin was washed with DMF, methanol, and DCM. A solution of dimethoxyacetaldehyde in DMF was added to the reaction mixture block and was shaken for 1 h at room temperature and a solution of $NaBH_3CN$ (3 equiv) in MeOH was added and shaken overnight. The reaction block was washed with DMF, MeOH, and then DCM.

4.4. Isocyanate coupling and cleavage

A solution of isocyanate (3 equiv) and DIPEA (3 equiv) in DCE was added to the resin and the reaction mixture was shaken for 5 h at room temperature. The reaction block was washed with DMF, MeOH, and then DCM. After the resin was vacuum dried, neat formic acid was treated and shaken at 50 °C for 3 h. After the resin was removed by filtration, the filtrate was condensed under reduced pressure using Speedvac [Thermo Savant] to give the product as a film. The product was diluted with 50% water/acetonitrile and then lyophilized after freezing, which yielded a pale yellow solid.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.07.051.

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14. Crystal data for compound **10**: $C_{19}H_{21}N_3O_4$ (295 K). $M = 355.39$, orthorhombic, space group $P2_12_12_1$, $a = 7.3195(9)$ Å, $b = 10.6543(12)$ Å, $c = 22.9191(15)$ Å, $V = 1787.3(3)$ Å^3, $Z = 4$, $\rho_{\text{calcd}} = 1.321$ g/cm^{-3}, absorption coefficient $= 0.094$ mm^{-1}, total reflections collected 3728, unique 2016 ($R_{\text{int}} = 0.0444$), GOF $= 1.027$, $R_1 = 0.0452$, $R_w = 0.0833$ ($I > 2\sigma(I)$). CCDC reference numbers 611436.
15. The suspected opposite stereoisomer (*R* diastereomer) was synthesized in less than 10% yield along with *S* diastereomer **10**. The molecular connectivity of *R* diastereomer was verified by NMR (^{1}H, COSY, HSQC) and Mass Spectroscopy, but we failed to confirm the definitive stereochemistry of *R* diastereomer, because it was not crystallized for X-ray crystallographic study.