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Pictet–Spengler synthesis of tetrahydro-β-carbolines using vinylsulfonylmethyl resin

Richard V. Connors, Alex J. Zhang and Stephen J. Shuttleworth*

Tularik Inc., Two Corporate Drive, South San Francisco, CA 94080, USA

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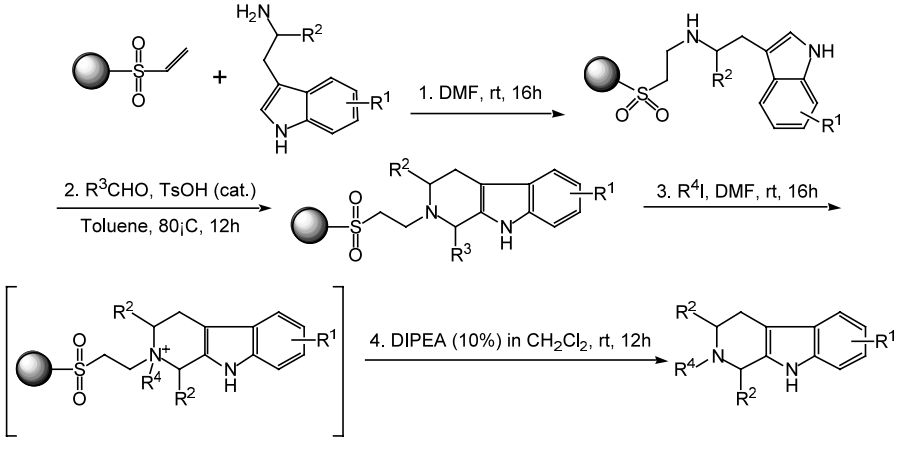
Abstract—A novel, solid phase Pictet–Spengler synthesis has been developed using vinylsulfonylmethyl resin. A library of 800 structurally diverse tetrahydro-β-carbolines was prepared in a four-step sequence starting from tryptamines. The final resin cleavage step enabled the introduction of a basic tertiary amine in the six-membered heterocyclic ring. © 2002 Elsevier Science Ltd. All rights reserved.

The Pictet–Spengler reaction is a valuable synthetic procedure in organic chemistry, having proven to be particularly useful for the preparation of alkaloids derived from indole and isoquinoline.[1,2] Over recent years, a number of articles outlining solid phase Pictet–Spengler routes to tetrahydro-β-carbolines have appeared.[3–10] It is noteworthy that in all of these reports, with the exception of one example using polymer-supported peptide aldehydes,[3] tryptophan derivatives were used as substrates, with the tryptophan carboxyl group serving as the means of attachment to the resin.[4–10]

Tetrahydro-β-carbolines constitute an important class of compounds in Medicinal Chemistry; indeed a search of the World Drug Index reveals 222 citations of these compounds in a number of therapeutic areas.[11] As part of a parallel synthesis exercise, we wished to prepare a collection of tetrahydro-β-carbolines using solid phase synthesis. Important prerequisites of our strategy, however, were that tryptamines be employed as the substrates and that the target compounds contain a basic tertiary amine in the six-membered heterocyclic ring. In view of the limited literature precedent for such a strategy, we turned our attention to developing a novel



Scheme 1.

* Corresponding author. E-mail: sshuttleworth@tularik.com

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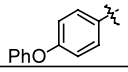
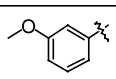
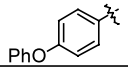
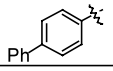
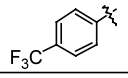
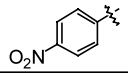
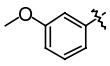
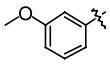
solid phase Pictet–Spengler synthesis using vinylsulfonylmethyl resin, which had previously been used successfully in the synthesis of tertiary amines libraries.[12]

Scheme 1 outlines the synthetic route developed. A collection of tryptamines was initially supported onto solid phase courtesy of a 1,4-addition to vinylsulfonylmethyl resin.[13] The supported substrates were subsequently treated with a range of aromatic aldehydes; the optimum conditions determined for this step were 80°C in the presence of *p*-toluenesulfonic acid monohydrate. This was followed by treatment with alkyl halides, and Hoffman elimination mediated by Hünig's base to furnish the desired products. Since the overall process was conducted on solid phase, excess reagents were used to drive each step to completion, and were then removed

Table 1.

Entry	R^1	R^2	R^3	R^4	Conversion (%)[15]
1	H	H		CH_3	88
2	H	H		CH_3	89
3	H	H		CH_3	81
4	H	H		CH_3	95
5	5-CH_3	H		CH_3	82
6	5-CH_3	H		CH_3	86
7	5-CH_3	H		CH_3	99
8	5-CH_3O	H		CH_3	88
9	5-F	H		CH_3	88
10	5-F	H		CH_3	82
11	7-CH_3	H		CH_3	84
12	7-CH_3	H		CH_3	91
13	7-CH_3	H		CH_3	86
14	7-CH_3O	H		CH_3	93
15	7-CH_3O	H		CH_3	91
16	H	CH_3		CH_3	81
17	H	CH_3		CH_3	87

by rigorous washing to furnish the tetrahydro-β-carboline products with good conversion. Based upon the results obtained, the steric and electronic nature of the tryptamine and aldehyde substituents did not appear to have a significant effect on the overall success of the cyclization reaction.

Procedure for library production

Stage 1—Tryptamine immobilization: Vinylsulfonylmethyl polystyrene resin (100 mg, 1.10 mmol/g, 0.11 mmol) was added to each well of a 48-well Teflon FlexChem reaction block.[14] Stock solutions (0.22 M) of tryptamines #1–8 were prepared in DMF. Tryptamine stock solution #1 (1.5 mL, 0.33 mmol) was added to each well in column 1. Tryptamine stock solutions #2–8 were added to columns 2 through 8 in similar fashion. The block was then sealed and agitated for 16 h at room temperature. Excess reagents were subsequently drained away and the resin was washed three times each with *N*,*N*-dimethylformamide, dichloromethane and toluene.

Stage 2—Pictet–Spengler cyclization: Stock solutions (0.55 M) of aldehydes #1–6 were prepared in toluene. Aldehyde stock solution (2 mL, 1.1 mmol) #1 was added to each well in row A of the 48-well block used in the previous step. Aldehyde stock solutions #2–6 were added to rows B through F in similar fashion. Each well was subsequently charged with toluenesulfonic acid monohydrate (2 mg, 0.011 mmol). The block was then sealed and agitated for 12 h at 80°C. Thereafter, the excess reagents were drained and the resin was washed three times each with *N*,*N*-dimethylformamide, methanol, Hünig's base (10%) in *N*,*N*-dimethylformamide, methanol, and again with *N*,*N*-dimethylformamide

Stage 3—Alkylation: Methyl iodide (2 mL of a 1 M solution in *N*,*N*-dimethylformamide) was added to each well of the 48-well block. The block was then sealed and agitated for 16 h at rt. The excess reagents were subsequently drained away and resin was washed with *N*,*N*-dimethylformamide, methanol and dichloromethane.

Stage 4—Cleavage: Hünig's base (2 mL of 10% solution in dichloromethane) was added to each well of the 48-well block. The block was then sealed and agitated for 12 h at rt. The cleavage products were obtained by filtration into a 48-well daughter plate, and were analyzed by HPLC-MS.[15] Following concentration using a vacuum centrifuge,[16] products with purities less than 80% were re-dissolved in dimethylsulfoxide and were purified by high-throughput preparative HPLC.[17] A selection of data is listed in Table 1, in which methyl iodide was used in the alkylation step.

In summary, a new synthetic route to tetrahydro-β-carbolines using vinylsulfonylmethyl polystyrene as a solid support has been developed. The approach complements those routes developed previously that employ solid-supported tryptophan esters and amides or peptide aldehydes as substrates, and is a sufficiently robust and versatile method to enable the production of a diverse set of compounds based upon the tetrahydro-β-carboline core.

Acknowledgements

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References

1. Pictet, A.; Spengler, T. *Chem. Ber.* **1911**, *44*, 2030.
2. Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.
3. Groth, T.; Meldal, M. *J. Comb. Chem.* **2001**, *3*, 45.
4. Kalijuste, K.; Undén, A. *Tetrahedron Lett.* **1995**, *36*, 9211.
5. Yang, L.; Guo, L. *Tetrahedron Lett.* **1996**, *37*, 5041.
6. Mohan, R.; Chou, Y.-L.; Morrissey, M. M. *Tetrahedron Lett.* **1996**, *37*, 3963.
7. Mayer, J. P.; Bankaitis-Davis, D.; Zhang, J.; Beaton, G.; Bjergarde, K.; Andersen, C. M.; Goodman, B. A.; Herrera, C. J. *Tetrahedron Lett.* **1996**, *37*, 5633.
8. Wang, H.; Ganesan, A. *Org. Lett.* **1999**, *1*, 1647.
9. Dondas, H. A.; Grigg, R.; MacLachlan, W. S.; MacPherson, D. T.; Markandu, J.; Sridharan, V.; Suganthan, S. *Tetrahedron Lett.* **2000**, *41*, 967.
10. Li, X.; Zhang, L.; Zhang, W.; Hall, S. E.; Tam, J. P. *Org. Lett.* **2000**, *2*, 3075.
11. World Drug Index available from Derwent Information Systems Inc.
12. Kroll, F. E. K.; Morphy, R.; Rees, D.; Gani, D. *Tetrahedron Lett.* **1997**, *38*, 8573.
13. Available from Novabiochem Inc.; catalogue number 01-64-0258.
14. Available from Robbins Scientific Inc.; see www.robsci.com.
15. An Agilent 1100 LC/MSD VL ESI system was used; percent conversions to desired products were determined at 254 nm.
16. A Genevac Series II HT4 centrifugal vacuum evaporator was employed; see www.genevac.com.
17. A Parallex Flex purification system from Biotage Inc. was employed; see www.biotage.com.