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Formal synthesis of the piperidine alkaloid (±)-prosophylline using polymer-supported dihydro-2*H*-pyridin-3-one

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Abstract—The use of polymer-supported 2,6-disubstituted-dihydro-2*H*-pyridin-3-one, as the 'polymorphic' core molecule for the formal synthesis of the piperidine alkaloid (±)-prosophylline is presented.

Combinatorial chemistry and solid-phase synthesis constitute two strategies, which offer several advantages compared with classic solution phase chemistry. Hence they are used increasingly often for the synthesis of simple or more complex designed bioactive structures as well as natural products and derivatives thereof.[1–3] Recently, our group has demonstrated the use of a polymer-supported polymorphic core molecule for the generation of libraries of pharmacophoric 'privileged structures'. Thus, 2*H*-pyran-3(6*H*)-one, after subjection to both skeletal and functional group manipulations gave a number of structurally diversified oxa-carbocycles.[4]

Here we report that the above concept can be expanded to encompass aza-carbocycles, such as piperidines, by exploiting polymer-supported 2,6-disubstituted-1,2-dihydro-2*H*-pyridin-3-one as the key intermediate. Substituted piperidines exhibit interesting biological activities and have served as precursors for the synthesis of various medicinally important piperidine alkaloids.[5] In order to validate the above proposition, (±)-prosophylline (**1**) was selected as the target molecule. This natural product has been isolated from various *Prosopis* species[6] among other 2,3,6-substituted piperidine alkaloids, which have been found to possess significant biological properties such as antibiotic and anaesthetic.[7–9] Several total syntheses towards prosophylline, both racemic and asymmetric, have been reported with overall yield from 9.2% to 12%.[5,10–13]

According to Scheme 1, (±)-prosophylline (**1**) could be derived from the solid supported advanced intermediate **2** after cleavage from the resin, reduction of the double bonds and removal of all the protecting groups. Compound **2** is closely related to the polymer-supported 1,2-dihydro-2*H*-pyridin-3-one **3**, which can be prepared through aza-Achmatowicz rearrangement of the corresponding furylamide **4**,[5,14] using appropriate oxidants (such as *m*-CPBA, PCC and NBS).[15–18] The synthesis of this furylamide would exploit previous experience in our group involving the coupling of Merrifield resin with azide **5** and subsequent reduction of the azide group. The alkoxy-benzyl ether linker thus formed, could be cleaved under mild conditions using DDQ at a later stage of the synthesis.[4,19]

Thus, furyl alcohol **6**[4] was treated with diphenyl phosphoryl azide (DPPA) in the presence of DBU to afford the corresponding azide[20] (Scheme 2). Cleavage of the silyl ether using TBAF gave the desired furylazide **5**, quantitatively. Coupling of **5** with Merrifield resin, reduction of the azide under Staudinger conditions (PPh_3, THF/H_2O) and tosyl protection of the resulting amine, afforded furylamide **4**. This amide was then subjected to oxidative cyclization using *m*-CPBA and the solid supported dihydropyridinone so formed was

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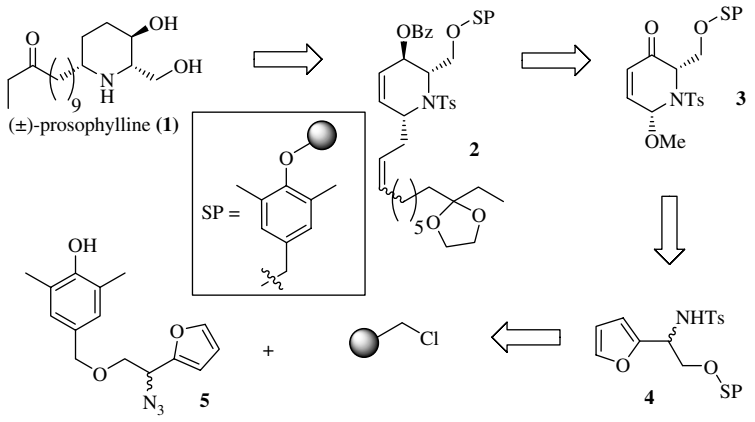
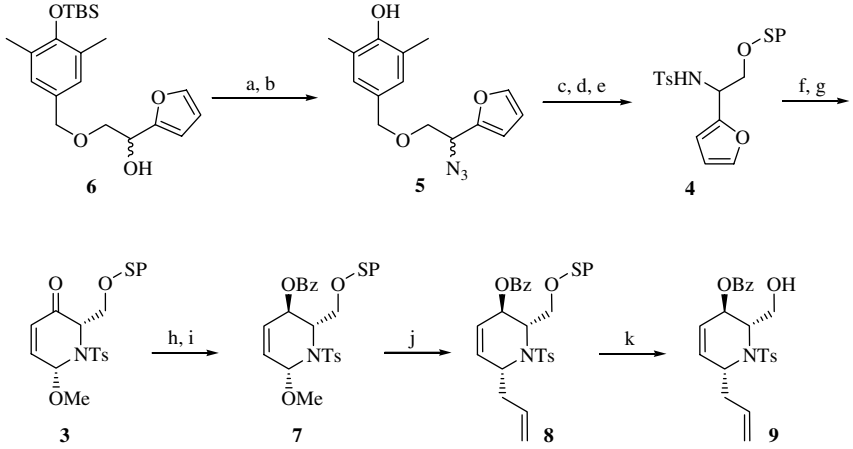


Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) DPPA, DBU, toluene, 65%; (b) TBAF, THF, 0 °C, 99%; (c) Merrifield resin, Cs_2CO_3, Bu_4NI, CH_2Cl_2, 3 d, 91%; (d) PPh_3, THF/H_2O 95:5, 60 °C; (e) *p*-TsCl, Et_3N, CH_2Cl_2; (f) *m*-CPBA, CH_2Cl_2; (g) $CH(OCH_3)_3$, $BF_3{\cdot}Et_2O$, THF, 0 °C to rt; (h) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, THF/MeOH 3:1, −30 to 0 °C; (i) Benzoic acid, PPh_3, DIAD, THF; (j) allyltrimethylsilane, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C; (k) DDQ, CH_2Cl_2/H_2O 20:1.

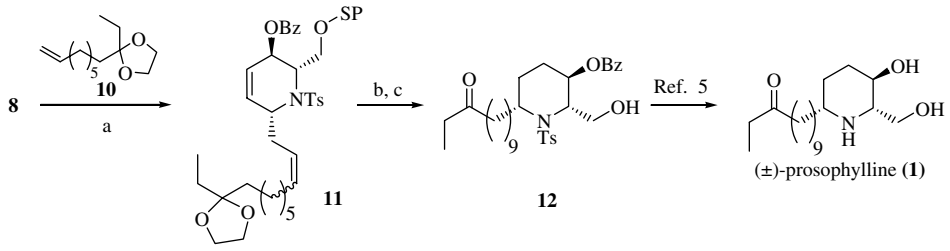
treated with trimethyl orthoformate in the presence of a Lewis acid to afford methyl ether **3**. Reduction under slightly modified Luche conditions at −30 °C[21] followed by Mitsunobu esterification yielded intermediate **7**, which was transformed into the corresponding allyl derivative **8** in the presence of allyl trimethylsilane and $BF_3{\cdot}Et_2O$ as a Lewis catalyst.[†] The relative stereochemistry of allyl alcohol **9**[22] (generated upon cleavage from the resin using DDQ) was established by 2D-NMR experiments and was in accordance with the literature (Scheme 2).[23]

With the advanced intermediate **8** in hand, the cross metathesis reaction with alkene **10**[24] was the next crucial step. The same approach was successfully followed by Cossy et al. for the solution phase synthesis of (−)-prosophylline.[12] Our goal was to extend this method by exploiting the advantages of the cross metathesis reaction on solid-phase.[25,26] After extensive experimentation,[27] it was found that four reaction cycles (using the Grubbs' 1st generation catalyst) were necessary in order to achieve optimum yields (Scheme 3).

Treatment of resin **11** with DDQ in a mixture of CH_2Cl_2/H_2O 20:1 not only resulted in the cleavage of the desired product from the resin but also the removal of the acetal protective group to afford (after reduction of the double bonds) keto-alcohol **12**[28] (Scheme 3). Conversion of the latter to (±)-prosophylline (**1**) has been already published by Haroutounian et al.[5] The total yield for this nine step synthesis on solid-phase was 12.8%.

In conclusion, we have developed a concise and effective solid-phase strategy for the synthesis of the alkaloid (±)-prosophylline. This strategy should be suitable for the production of diverse derivatives of **1** either by using different side-chains during the cross metathesis reaction or by skeletal manipulations in the early stages of the synthesis.

[†] The use of $TiCl_4$ as a Lewis catalyst resulted in partial cleavage of **8** from the resin even at −78 °C.



Scheme 3. Reagents and conditions: (a) Alkene **10**, Grubbs' 1st generation catalyst, CH_2Cl_2, 35 °C, four cycles; (b) DDQ, CH_2Cl_2/H_2O 20:1, 12.8% (for nine steps); (c) H_2/Pd, MeOH, 99%.

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20. *Spectral data for TBSO-***5**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.4 (m, 1H), 6.94 (s, 2H), 6.35 (m, 2H), 4.68 (dd, 1H, $J = 7.5$, 5.0 Hz), 4.47 (ABq, 2H, $J = 11.6$ Hz, $\Delta\nu = 24.8$ Hz), 3.81 (dd, 1H, $J = 10.1$, 5.0 Hz), 3.78 (dd, 1H, $J = 10.1$, 7.6 Hz), 2.21 (s, 6H), 1.04 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.8, 130.0, 128.5, 110.4, 108.4, 73.4, 70.5, 58.4, 26.1, 19.8, 17.8, −2.5.
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22. *Spectral data for* **9**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, 2H, $J = 7.9$ Hz), 7.57–7.51 (m, 1H), 7.40–7.33 (m, 4H), 7.00 (d, 2H, $J = 7.9$ Hz), 6.16 (dd, 1H, $J = 10.4$, 3.6 Hz), 5.94–5.82 (m, 2H), 5.24 (d, 1H, $J = 5.7$ Hz), 4.49 (t, 2H, $J = 9.4$ Hz), 4.38 (t, 1H, $J = 7.8$ Hz), 3.85–3.76 (m, 1H), 3.70–3.61 (m, 1H), 2.86–2.78 (m, 1H), 2.35 (ddd, 1H, $J = 18.9$, 12.4, 9.6 Hz), 2.29 (t, 1H, $J = 5.8$ Hz), 2.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.1, 143.3, 137.5, 133.8, 133.1, 132.5, 129.7, 129.6, 128.1, 127.1, 120.1, 118.7, 65.4, 62.9, 56.9, 52.9, 42.8, 21.5; HRMS *m/z*: [M+Na$^+$] Calcd for $C_{23}H_{25}NO_5SNa$: 450.1351; found, 450.1310.
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24. Compound **10** was prepared in the same manner as reported in Ref. 12. Furthermore, the respective ketone was protected as a ketal by treatment with 2-methyl-2-propyl-1,3-dioxolane and a catalytic amount of CSA at 40 °C.
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27. For the determination of conversion and yield of this reaction, a sample was subjected to cleavage conditions (DDQ, CH_2Cl_2/H_2O 20:1) and after small column purification for the removal of the excess of **10** and its self coupling product, the ratio of unreacted material vs product was judged by ^{1}H NMR.
28. *Spectral data for* **12**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69–7.52 (m, 5H), 7.40–7.32 (m, 2H), 6.95 (d, 2H, $J = 8.4$ Hz), 5.11 (m, 1H), 4.21 (m, 1H), 4.05 (m, 1H), 3.82 (d, 2H, $J = 7.3$ Hz), 2.47–2.36 (m, 4H), 2.13 (s, 3H), 2.00–1.15 (m, 20H), 1.04 (t, 3H, $J = 7.3$ Hz); HRMS (as ketal with ethylene glycol) *m/z*: [M+Na$^+$] Calcd for $C_{34}H_{49}NO_7SNa$: 638.3128; found, 638.3118.