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Asymmetric Synthesis

Consecutive Pictet–Spengler Condensations toward Bioactive 8-Benzylprotoberberines: Highly Selective Total Syntheses of (+)-Javaberine A, (+)-Javaberine B, and (−)-Latifolian A


Abstract: Enantiopure 8-benzylprotoberberines were synthesized by two consecutive Pictet–Spengler (PS) condensations with protected 3,4-dihydroxyphenylacetaldehydes. The first PS to (+)-(R)-norprotosinomenine was optimized to 90 % ee with 5 mol-% of (R)-TRIP as chiral Brønsted acid (> 99 % ee after trituration). The second PS did not require any catalyst, and its regioselectivity was strongly dependent on the solvent: 99:1 ortho selectivity was obtained in trifluoroethanol leading to (+)-javaberine A; 81:19 para selectivity was reached in apolar aprotic solvents for the synthesis of (+)-javaberine B. Complete, natural diastereoselectivity was observed in the second PS. Through selective catechol oxidation the spirocyclic alkaloid (−)-latifolian A was prepared from protected (+)-javaberine A.

Introduction

The 1-benzyltetrahydroisoquinoline structure forms the basis for a large number of pharmaceuticals with a diverse mode of action.[1] Biological activity was observed on dopamine-related CNS receptors, but also applications such as antitumor, antimicrobial, antifungal and anticholinesterase agents were reported.[2] Tetrahydropseudoberberines (THPBs) contain an additional methylene group to form a dibenzoquinolizidine ring system (Figure 1). An extensive range of biological activities was reported for these alkaloids. To mention a few examples, C-8-unsubstituted (−)-(S)-stepholidine (1) displays an interesting profile on the dopamine D1 and D2 receptors and has potential antipsychotic and antinoceptive activity.[3] Isocorypalmine (2) was developed as anticoagulant therapeutic.[4] THPBs containing a substituent at the 8-position are less abundant in nature but were also reported to display interesting biological activity.[5] The regioisomers (+)-javaberine A (3) and B (4) contain a third catechol-type aromatic ring and show a strong inhibitory effect on the lipopolysaccharide-induced tumor necrosis factor.[6] The spirolk alkaloid (−)-latifolian A (5, from Gnetum latifolium) has an additional carbon–nitrogen bond, making the nitrogen atom quaternary. This alkaloid was reported to inhibit JNK3 kinase, which plays a role during neuronal apoptosis.[7] Latifolian A (from Gnetum montanum) was reported to show antibacterial activity against methicillin-resistant Staphylococcus aureus.[8] In view of their interesting structures and highly relevant biological activity we have developed and report here efficient and scalable total syntheses of the natural enantiomers of javaberine A and B and the related latifolian A, based on our enantioselective chiral Brønsted acid catalyzed Pictet–Spengler methodology.[9]

Figure 1. Structures of tetrahydropseudoberberine (THPB) alkaloids.

Steroselective syntheses of tetrahydropseudoberberine alkaloids by C-ring construction require asymmetric 1-benzyltetrahydroisoquinolines as starting materials. Several synthetic methods are known for the enantioselective preparation of 1-benzyltetrahydroisoquinolines.[10] Most frequently Bischler–Napieralsky methodology is used, including asymmetric imine hydrogenation.[11,12] Biocatalytic production of 1-benzyltetrahydroisoquinolines with high enantiomeric purity is becoming increasingly important, and recently several efficient examples of use of the Pictet–Spenglerase norcoclaurine synthase (NCS) were reported.[12–14]

The formation of the C-ring of 8-unsubstituted THPBs, e.g. xylopinine (8, Scheme 1), is readily performed with formaldehyde and acid at elevated temperatures leading to para substitution towards the oxygen substituent at C-11 in the D-ring. However, in many natural, bioactive THPBs, such as stepholidine (1), isocorypalmine (2), javaberine B (4), and scoulerine (6), an oxygen substituent is present at the C-9 ortho position in the...
Results and Discussion

We started our synthetic approach with the Pictet–Spengler condensation of 9 with protected dopal (dihydroxyphenylacet-aldehyde, 10)[9a] as is shown in Scheme 2. A screening to improve the reaction conditions and catalyst loading gave the unexpected observation that lowering from 10 mol-% to 5 mol-% gave a slight improvement of the ee to a reproducible 90 %. A possible explanation could be the quick formation of enamines 11 with concomitant release of water. Water coordinates to the TRIP/iminium ion pair and has a negative influence on the enantioselectivity.[9] Lower catalyst loading slows down the reaction and allows water to bind to the drying agent sodium sulfate before the enantioselective cyclization takes place. Further lowering of the catalyst loading to 3 mol-% did not change the ee, but the reaction did not reach completion after 3 d at room temperature. The role of (S)-BINOL as a cocatalyst remains unclear, but is substantial.[9a,9b] After selective removal of the Nps group from 12, enantiopure (R)-13 was isolated in good yield as a highly insoluble compound by simple trituration. Removal of the TBS group from 13 readily occurred with ammonium fluoride in methanol to yield (+)-(R)-norprotosinomenine (14), the precursor for the second Pictet–Spengler condensation. The free phenolic OH group in 14 was essential for a smooth cyclization and made heating and strong acids unnecessary. As the aldehyde TBS-protected dopal 10 was again chosen for its low polarity and relative stability compared to dopal itself. From initial screening experiments it became clear that the regioselectivity of this reaction was greatly determined by the solvent. Catalysts such as (R)- or (S)-TRIP and thiourea catalysts slowed down the reaction and gave incomplete reactions with a slight para preference. Table 1 shows the influence of several solvents on the ortho/para regioselectivity of the Pictet–Spengler condensation between 10 and 14. The increasing H-bond donating character of the solvent matched with the amount of para-substituted product 16, ending with hexafluoro-2-propanol and trifluoroethanol as equally effective (water was not tested for solubility reasons). Addition of acetic acid to DCM as solvent had little effect on the product distribution (ca. 1:1) and also decreased the reaction rate (Entries 1 and

Scheme 2. Reaction conditions: (a) (R)-TRIP (5 mol-%), (S)-BINOL (20 mol-%), Na₂SO₄, toluene, room temp., 3 d, 85 %, 90 % ee; (b) concd. aq. HCl, PhSH, DCM/EtOH, -15 °C, then trituration, 68 %, > 99 % ee; (c) NH₄F, MeOH, 40 °C, 1 h, 99 %; (d) toluene/DCM (9:1), 0.02 ml, room temp., 3 d, 88 %, 71 % ee; (e) TFE, 0 °C, 3 h, 85 %; (f) 1 (1) Br₂, DCM, 0 °C, 3 h, (2) neutralization with Et₃N/MeOH, 99 % from 16, 87 % from 15; (g) Ac₂O, pyridine, room temp., 3 h, 68 %; (h) 12 (90 % ee) for (R)-TRIP = (R)-3,3′-bis(2,4,6-trisopropylphenyl)-BINOL-phosphonic acid, (S)-BINOL = (S)-1,1′-bi(2-naphthol), TFE = 2,2,2-trifluoroethanol.
On a preparative scale the para selectivity was improved to 99:1 and the yield to 85% (Table 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>ortho/para (a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFE</td>
<td>0</td>
<td>3</td>
<td>&gt; 5:95 (1:99)</td>
</tr>
<tr>
<td>2</td>
<td>HFIP[c]</td>
<td>0</td>
<td>3</td>
<td>&gt; 5:95</td>
</tr>
<tr>
<td>3</td>
<td>methanol</td>
<td>0</td>
<td>3</td>
<td>11:89</td>
</tr>
<tr>
<td>4</td>
<td>ethanol</td>
<td>0</td>
<td>3</td>
<td>16:84</td>
</tr>
<tr>
<td>5</td>
<td>DCM (10 equiv. HOAc)</td>
<td>r.t.</td>
<td>18</td>
<td>45:55</td>
</tr>
<tr>
<td>6</td>
<td>DCM (2 equiv. HOAc)</td>
<td>r.t.</td>
<td>18</td>
<td>50:50</td>
</tr>
<tr>
<td>7</td>
<td>DCM</td>
<td>r.t.</td>
<td>18</td>
<td>55:45</td>
</tr>
<tr>
<td>8</td>
<td>MeCN</td>
<td>r.t.</td>
<td>18</td>
<td>65:35</td>
</tr>
<tr>
<td>9</td>
<td>DCE[c]</td>
<td>r.t.</td>
<td>18</td>
<td>70:30</td>
</tr>
<tr>
<td>10</td>
<td>toluene[d]</td>
<td>r.t.</td>
<td>3</td>
<td>80:20 (81:19)</td>
</tr>
</tbody>
</table>

Table 1. ortho/para selectivity in the cyclization of 14 (see Scheme 2).

(a) At > 80% conversion, determined by 2H NMR spectroscopy. (b) Preparative scale. (c) HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol, DCE = 1,2-dichloroethane. (d) 0.02 M, prepared by diluting a 0.5 M solution of HBr in acetic acid.

To optimize the formation of ortho product 15 aprotic, apolar solvents were required (Entries 9 and 11), and the solubility of the substrates was the only limitation here for further improvement. Finally an ortho/para ratio of 81:19 with 88% total yield was achieved using toluene and a 0.02 M substrate concentration.

To explain these strong solvent effects, we suggest that protic solvents coordinate to the hydroxy and alkoxy substituents of the substrates to turn these away from the reaction center, which allows the solvent to catalyze iminium ion formation. In apolar, aprotic solvents a transition state is suggested in which the phenolic OH group protonates the initially formed aminal (Scheme 3). Lowering of the concentration of the substrates decreases the chance of interference of intermolecular hydrogen bonding in the iminium salt formation.

Scheme 3. ortho-Selective Pictet–Spengler condensation.

Interestingly, the regioisomers obtained always had a trans relationship between H-8 and H-14, as it is in all three natural product targets. Even trace amounts (< 1%) of the undesired cis isomers were not observed.

In the final steps the OMe and OTBS groups were cleaved with boron tribromide, leading to the HBr salts of javaberine A (3) in 48% overall yield from 9 and of javaberine B (4) in 35% overall yield from 9 (Scheme 2). Complete NMR analysis was performed on these HBr salts, on the corresponding free bases and on the hexaacetates 17 and 18. The 1H and 13C NMR spectra of 3, 17, and 18 are identical to those in the literature.[6,22,23] Comparison of the sign of the optical rotations confirmed the absolute configurations of the natural products as (8R,17S).[25] The literature [α]D20 values, however, were much lower: +112.5 (c = 0.40, CHCl3) for synthetic vs. -8.0 (c = 0.8, CHCl3) for natural javaberine B hexaacetate 17.[6a] The reasons for the remarkable differences in the magnitudes of the rotation values are unclear.

The synthesis of latifolian A (5) also started from (R)-norprotoberines (14) but required a change of protecting groups in the dihydroxyphenylacetaldehyde Pictet–Spengler partner. Double-TBS-protected dopal 22 will give a free catechol functionality after desilylation, while the other two catechol groups remain protected as mono-methyl ethers. TFE as a regioselective Pictet–Spengler solvent again afforded almost exclusively para-substituted phenol 23 in high yield. Desilylation to 23 and oxidation with PIFA[24] gave the spirocyclic quaternary ammonium salt 25 as its bis-methyl ether, which was deprotected with HBr in acetic acid to enantiopure latifolian A (5, Scheme 4).


The 1H and 13C NMR spectra fully confirmed the structure of 5. The sign of the rotation of our synthetic material ([α]D20 = -60 (c = 0.58, MeOH)) established the configuration of natural (–)-latifolian A as (7R,8R,14S) (reported value: [α]D20 = -33 (c = 0.21, MeOH)).[27] When a solution of javaberine A (3) in CD2OD was oxidized with PIFA in an NMR tube, the characteristic signals for H-8 and H-14 of latifolian A (5) appeared. This is not suitable as a synthetic method, however, because non-selective catechol oxidation could not be prevented.

Conclusions

Short and highly selective syntheses of the enantiopure title compounds were accomplished. Starting from Nps-protected amine 9 overall yields of 48% for (+)-javaberine A, 35% for (+)-javaberine B and 41% for (–)-latifolian A were accomplished; para selectivity in the second Pictet–Spengler cyclization was improved to almost 100:0 in protic solvents, but, more importantly, the ortho selectivity was directed to 80:20 by apolar solvents, which opens a route to many bioactive 9-alkoxytetrahydropyroperberines.

Keywords: Enantioselectivity · Chiral Brunsted acid catalysis · Pictet–Spengler reaction · Alkaloids · Regioselectivity