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

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] Tetrahydroprotoberberines (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] Iso Corypalmine (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 spiroalkaloid (–)-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]

Stereoisomeric syntheses of tetrahydroprotoberberine 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.[3,10,11] 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
D-ring. Because electrophilic-type cyclizations in general give preference for alkylation at the para position of the oxygen atom, these alkaloids are not readily available.

Along biosynthetic pathways, the berberine bridge enzyme (BBE)\(^\text{[15,16]}\) oxidizes the N-methyl group in e.g. (S)-reticuline ([S]-7, R = Me) to the iminium ion, which cyclizes at the ortho position of the D-ring to form 6. This process was efficiently applied by Kourotlik and co-workers for asymmetric THPB synthesis (Scheme 1).\(^\text{[10,17]}\)

Synthesis of THPBs with a substituent at the 8-position as in the javaberines (3 and 4, Figure 1) introduces diastereoselectivity as an additional complication, and only a few, nonselective examples are mentioned in the literature.\(^\text{[14,17a]}\) Recently, the synthesis of racemic javaberine A was described, using a Bischler–Napieralski C-ring closing approach followed by reduction, providing mainly the undesired C-8 epimer.\(^\text{[6b]}\)

The absolute configuration is an important issue/aspect in the synthesis of these alkaloids. In many biotransformations (S)-1-benzyltetrahydroisoquinolines and consequently (S)-tetrahydroprotoberberines are formed. Enzymes that produce or accept the isoquinoline (R) enantiomer are not readily available. Chiral Brønsted acid catalyzed Pictet–Spengler reactions are not limited to one enantiomer, and in particular, in the tetrahydro-β-carboline synthesis from indoles, enantioselectivity is well established.\(^\text{[9c,9d,20]}\) In our previous work on the enantioselective synthesis of tetrahydroisoquinolines (THIQs), we have shown that a sulfur substituent on the nitrogen atom (ortho-nitrophenylsulfenyl, Nps) as in (S)-TRIP/iminium ion, which cyclizes at the ortho position 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 3).

Results and Discussion

We started our synthetic approach with the Pictet–Spengler condensation of 9 with protected dopal (dihydroxyphenylacetalddehyde, 10)\(^\text{[9a]}\) as is shown in Scheme 2. A screening to improve the reaction conditions and catalyst loading gave the unexpected observation that lowering of the amount of (R)-TRIP from 10 mol-% to 5 mol-% gave a (slight) increase of the ee to a reproducible 90%. A possible explanation could be the quick formation of enamine 11 with concomitant release of water. Water coordinates to the TRIP/iminium ion pair and has a negative influence on the enantioselectivity. 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.\(^\text{[9a,9b]}\) 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 (+)-3,3′-bis(2,4,6-triisopropylphenyl)-BINOL-phosphoric acid, (S)-BINOL = (S)-1,1′-bi(2-naphthol), TFE = 2,2,2-trifluoroethanol.

Scheme 1. Regioselectivity in the tetrahydroprotoberberine C-ring construction.

Scheme 2. Reaction conditions: (a) (R)-TRIP (5 mol-%), (S)-BINOL (20 mol-%), NaN\(_2\), toluene, room temp., 3 d, 85 %, 90 % ee; (b) concd. aq. HCl, PhSH, DCM/EtOH, −15 °C, then trituration, 68 %, > 99 % ee; (c) NH\(_2\)F, MeOH, 40 °C, 1 h, 99 %; (d) toluene/DCM (9:1), 0.02 M, room temp., 3 d, 88 %, 71 % ee; (e) TFE, 0 °C, 3 h, 85 %; (f) (1) BBr\(_3\), DCM, 0 °C, 3 h, (2) neutralization with Et\(_3\)N/MeOH, 99 % from 13, 87 % from 15; (g) Ac\(_2\)O, pyridine, room temp., 3 h, 68 % 17, 46 % 18. (R)-TRIP = (R)-3,3′-bis(2,4,6-triisopropylphenyl)-BINOL-phosphoric 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 1. ortho/para selectivity in the cyclization of 14 (see Scheme 2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>T</th>
<th>t</th>
<th>ortho/para (^{[a]}) (15/16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFE</td>
<td>0 °C</td>
<td>3 h</td>
<td>&gt; 95:5 (1:99) (^{[b]})</td>
</tr>
<tr>
<td>2</td>
<td>HFIP (^{[c]})</td>
<td>0 °C</td>
<td>3 h</td>
<td>&gt; 5:95</td>
</tr>
<tr>
<td>3</td>
<td>methanol</td>
<td>0 °C</td>
<td>3 h</td>
<td>11:89</td>
</tr>
<tr>
<td>4</td>
<td>ethanol</td>
<td>0 °C</td>
<td>3 h</td>
<td>16:84</td>
</tr>
<tr>
<td>5</td>
<td>DCM (10 equiv. HOAc)</td>
<td>r.t.</td>
<td>18 h</td>
<td>45:55</td>
</tr>
<tr>
<td>6</td>
<td>DCM (2 equiv. HOAc)</td>
<td>r.t.</td>
<td>18 h</td>
<td>50:50</td>
</tr>
<tr>
<td>7</td>
<td>DCM</td>
<td>r.t.</td>
<td>18 h</td>
<td>55:45</td>
</tr>
<tr>
<td>8</td>
<td>MeCN</td>
<td>r.t.</td>
<td>18 h</td>
<td>65:35</td>
</tr>
<tr>
<td>9</td>
<td>DCE (^{[c]})</td>
<td>r.t.</td>
<td>18 h</td>
<td>70:30</td>
</tr>
<tr>
<td>10</td>
<td>toluene (^{[d]})</td>
<td>r.t.</td>
<td>3 d</td>
<td>80:20 (81:19) (^{[b]})</td>
</tr>
</tbody>
</table>

\(^{[a]}\) At > 80 % conversion, determined by \(^1\)H NMR spectroscopy. \(^{[b]}\) Preparative scale. \(^{[c]}\) HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol, DCE = 1,2-dichloroethane. \(^{[d]}\) 0.02M, prepared by diluting a 0.5 M solution of [1]

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 alkyl 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 19 in an intramolecular fashion to generate the iminium salt 20. In non-coordinating solvents this ion pair directs the cyclization to the ortho position (Scheme 3). Lowering of the concentration of the substrates decreases the chance of interference of intermolecular hydrogen bonding in the iminium salt formation.

Interestingly, the regiosomers 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 \(^1\)H and \(^13\)C 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,8R,14S). The literature \([\alpha]_D^20\) values, however, were much lower: +112.5 (c = 0.40, CHCl₃) for synthetic vs. +5.0 (c = 0.9, CHCl₃) for natural javaberine A hexaacetate 18 and +28.0 (c = 0.68, 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)-norprotonesinemonine (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).

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![Scheme 4. Synthesis of latifolian A (5). Reaction conditions: (a) TFE, 0 °C, 3 h, 92 %; (b) NH₄F, MeOH, 35 °C, 1 h, 99 %; (c) PIFA, DCM/TFE (1:1), 0 °C, 87 %; (d) 48 % aq. HBr, reflux, 3 h, 91 %, TFE = 2,2,2-trifluoroethanol, PIFA = bis(trifluoroacetoxy)iodo)benzene.](image)

The \(^1\)H and \(^13\)C NMR spectra fully confirmed the structure of 5. The sign of the rotation of our synthetic material \([\alpha]_D^{20} = –60 \text{ (c = 0.58, MeOH)}\) established the configuration of natural (–)-latifolian A as (7R,8R,14S) (reported value: \([\alpha]_D^{20} = –33 \text{ (c = 0.21, MeOH)}\) \(^{[7]}\). 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 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-alkoxytetrahydropyrotoberberines.

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


For a recent example, including a complete literature overview, see: N. Mittal, D. X. Sun, S. Deidel, Org. Lett. 2014, 16, 1012–1015.


After neutralization to the free base, chemical shift deviations were observed when comparing synthetic to natural javaberine A. By adding TEA portionwise to a solution of the HBr salt in CD2OD in an NMR tube, this discrepancy was solved: both compounds described in literature were measured as partial salts, possibly TFA salts from HPLC separations. It should be noted that the free bases have a strong tendency to darken when exposed to air and/or light, comparable to dopamine. Complete or partial salt formation protects these polyphenols (see the Supporting Information).

Javaberine B (3) was not isolated in pure form from the plant extract, but was obtained as its hexacacetate 17(A).

DDQ oxidation is also suitable, but removal of the side product DDQ-H2 was problematic.