The Palladium-Catalyzed Preparation of Condensed Tetracyclic Heterocycles and their Application to the Synthesis of *rac*-Mangochinine

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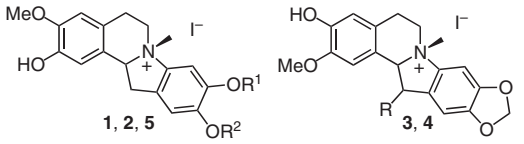
Dedicated to Prof. György Hajós on the occasion of his 60th birthday.

Abstract: Dihydroisoquinoline derivatives and their analogues, prepared by the Bischler–Napieralsky reaction, were converted to their indole-fused derivatives. Scope and limitations of the palladium-catalyzed reaction, proceeding through the tautomeric enamine forms of these compounds, were studied and the process was extended to the preparation of racemic mangochinine.

Key words: ring closure, palladium, catalysis, indoles, natural products

Introduction

Following the isolation of the first dibenzopyrrocoline alkaloids, cryptaustoline (**1**) and cryptowoline (**2**), from *Cryptocaria bowiei* by Ewing,[3] reports on the isolation and characterization of related natural products cryptowolidine (**3**), cryptowolinol (**4**) were also published.[4] A more recent study of the bark of *Manglietia chingii*, used in traditional Chinese medicine revealed the presence of another member of this family, mangochinine (**5**) in it[5] (Figure 1). Besides their use in natural remedies, the antileukemic and antitumor[6,7] activity and curare-like paralytic action[8] of benzopyrrocoline alkaloids were also reported.



1 cryptastoline $R^1 = R^2 = Me$
2 cryptovoline $R^1 = R^2 = -CH_2-$
5 mangochinine $R^1 = Me$, $R^2 = H$

3 cryptovolidine R = H
4 cryptovolinol R = OH

Figure 1 Mangochinine and related dibenzopyrrocoline alkaloids

The first reports on the preparation of the dibenzopyrrocoline core by Robinson[9] and Schöpf[10] were the results of an unexpected transformation in both cases. These reports preceded the isolation of the natural products, although, based on the ease of their formation, Schöpf had predicted the presence of this framework in natural sources.[10] The first total synthesis of dibenzopyrrocolines was reported by Kametani and co-workers,[11] who prepared racemic cryptaustoline (**1**) and cryptowoline (**2**) by an intramolecular aromatic nucleophilic substitution, while the absolute stereochemistry of **1** has been established as *R*-(–) by Meyers.[12]

Kametani's process, carried out in the presence of a strong base, probably proceeds through a benzyne intermediate. This strategy was successfully extended by Kano also to the synthesis of indolo[2,1-*a*]benzazepine and quinolino[2,1-*a*]benzazepine derivatives.[13,14] A recent development in this direction, reported by Orito and co-workers, is the formation of the tetracycle in the nucleophilic substitution of a tautomeric form, achieved by prolonged heating (3–4 days) of the appropriate dihydroisoquinoline derivatives in DMF at 140 °C in the presence of potassium carbonate.[15] The authors used this methodology to prepare the racemic form of cryptaustoline (**1**) and cryptowoline (**2**). Their attempts to extend the procedure to other ring systems, however, remained in vain.

Following Kametani's report several other methods were published for the preparation of the dibenzopyrrocoline core, including radical cyclizations[16]and silicon-mediated ring-closure reactions.[17] Recently Nolan and co-workers replaced Kametani's aryne reaction by the Buchwald–Hartwig coupling to achieve the efficient synthesis of **1** and **2**.[18] The key to their success in the ring-closure reaction was the use of N-heterocyclic carbenes as supporting ligands with palladium.

As most other groups, we also planned to follow the well established 'dihydroisoquinoline route' in our synthetic efforts. Our aims were i) to test the scope of the palladium-catalyzed preparation of dibenzopyrrocoline derivatives; and ii) to utilize the gathered experience in the synthesis of mangochinine (**5**).

The key step in our strategy (Scheme 1) is the palladium-catalyzed C–N bond formation reaction, which would require the use of appropriately substituted tetrahydro-, or dihydroisoquinoline derivative **6**. The preparation of compounds like **6** is very well established in the literature by the Bischler–Napieralsky ring-closure reaction, following the acylation of the appropriate phenethylamine **8** analogue with a brominated phenylacetic acid derivative **7**. An important point in the early stage of synthesis is the choice and introduction of protecting groups. A practical feature of the envisaged approach is the fact that both **7** and **8** might be traced back to the same, easily available

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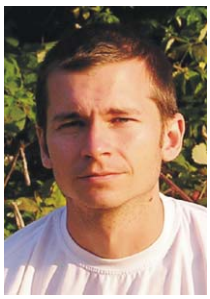
Biographical Sketches



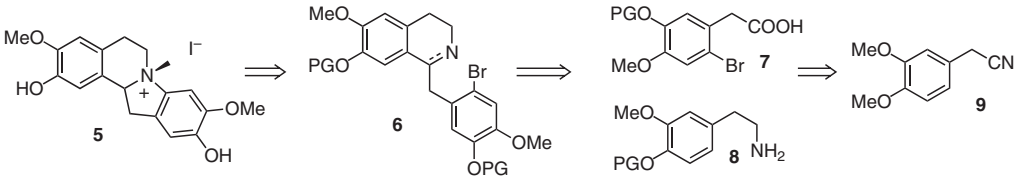
Zoltán Vincze was born in 1974. He studied chemistry at the Eötvös Loránd University and worked for his M.Sc. degree (1999) under the guidance of András Kotschy. He is finishing his Ph.D. thesis with András Kotschy and Péter Nemes on up-to-date preparative methods in the synthesis of different condensed isoquinoline derivatives. He is currently an assistant professor in the Institute of Chemistry at the Faculty of Veterinary Sciences, Szent István University. His research interests include transition-metal catalysis and microwave-mediated transformations in heterocyclic chemistry.

Andrea Beatrix Bíró was born in Kolozsvár (Cluj, Romania) in 1978. After studies at the Babes Bolyai University in Kolozsvár, she received her Master of Science degree in 2002 under the supervision of Dr. Silaghi Luminita. Since 2002 she is a Ph.D. student at Eötvös Loránd University (Hungary), where she is about to complete her thesis on the transition-metal-catalyzed transformations of heterocyclic systems under the supervision of András Kotschy.

Márton Csékei was born in Pécs (Hungary) in 1980. After receiving his M.Sc. degree at Eotvos Lorand University, he became a Ph.D. student under the supervision of Dr. András Kotschy. His interests include the synthesis of natural products containing the benzofuran framework and the preparation of tetrazine derivatives. At present he is doing an internship at BASF in Ludwigshafen (Germany).

Géza Timári received his diploma at Eötvös University in Budapest 1979, and his Ph.D. at the same university in 1983. In 1984, he joined the group of Prof. A. Messmer at the Central Research Institute for Chemistry, Hungarian Academy of Sciences (HAS) and obtained the Candidate of Sciences degree from the HAS in 1993. He moved to the pharmaceutical company Chinoin (Budapest) in 1998, where he is currently head of Medicinal Chemistry Laboratory I. In 1988 he joined the laboratory of Prof. S. Gronowitz for a year at the University of Lund, Sweden, where he worked on transition-metal-catalyzed cross-coupling reactions. He also spent one year (1994) at the University of Geneva (Switzerland) in the group of Prof. C. W. Jefford and worked on the amplified asymmetric dihydroxylation methodology. In 1995, as a Volkswagen Fellow, he joined Prof. E. Winterfeldt's group at the University of Hannover carrying out natural product synthesis. His research interests include the synthesis of biologically active molecules using organometallic approaches and asymmetric synthesis.

András Kotschy was born in 1969. He studied chemistry at the Eötvös Loránd University and worked for his M.Sc. (1992) and Ph.D. (1995) degrees with András Messmer and György Hajós at the Central Research Institute for Chemistry of the Hungarian Academy of Sciences. He started his independent carrier at the Institute of Chemistry at Eötvös Loránd University, where following two years of postdoctoral stay (1996 – Royal Society Postdoctoral Fellow with David Smith in St Andrews, and 1999 – Alexander von Humboldt Research Fellow with Paul Knochel in München) he has been an Associate Professor since 2002. He received his habilitation from the same institution in early 2005. His research interests span different aspects of heterocyclic chemistry from the preparation and functionalization of heterocycles through the understanding of their chemical behavior, to their application in catalysis and molecular recognition.



Scheme 1 Retrosynthetic analysis for the preparation of mangochinine (**5**)

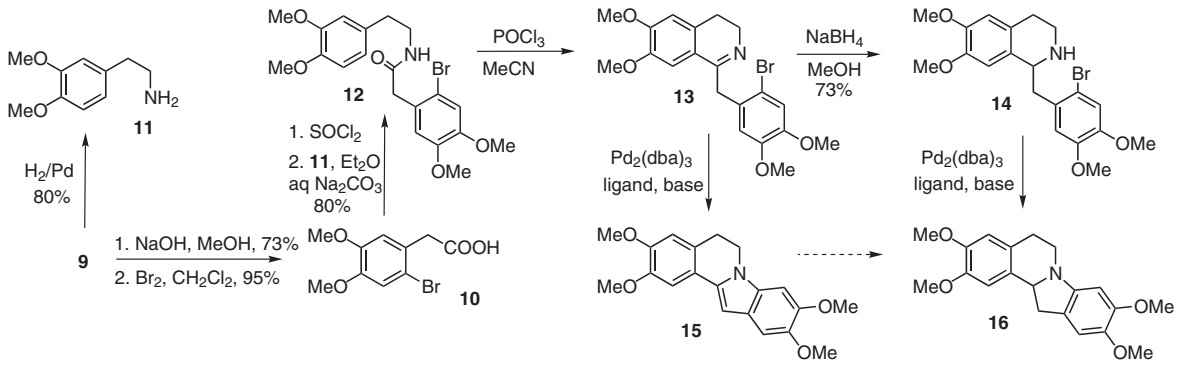
starting material, 3,4-dimethoxyphenylacetonitrile (**9**), also known as homoveratronitrile.

Results and Discussion

The first experiments were directed at testing the feasibility of the planned synthetic route. To simplify our synthesis we selected such analogues of **6**–**8** as model systems that contained only methoxy groups. 3,4-Dimethoxyphenylacetonitrile (**9**, homoveratronitrile) was converted to 2-bromo-4,5-dimethoxyphenylacetic acid (**10**) by hydrolysis and bromination in good yield.[19] Reduction of **9** under heterogeneous conditions yielded the other required reagent **11** in good yield. Acylation of **11** with the acid chloride prepared from **10** and thionyl chloride gave the desired amide **12** in good yield,[20] which was converted to the dihydroisoquinoline derivative **13** in Bischler–Napieralsky reaction in acetonitrile.[6] Reduction of **13** to the appropriate tetrahydroisoquinoline derivative **14** with sodium borohydride also proceeded readily[13] (Scheme 2). At this stage we had two alternate entry points to the formation of the tetracyclic core. We could either follow the route pioneered by Nolan[18] and convert **14** to **16**, or we could also try to extend Orito's methodology[15] and attempt to convert **13** to **15** using transition metal catalysis. This latter transformation would involve a Buchwald–Hartwig coupling through a tautomeric form of **13**, which is not unprecedented in the literature for bicyclic systems. The conversion of arylhydrazones to indole derivatives[21] and the preparation of benzofuran derivatives[22] utilizing such a sequence were both reported recently.

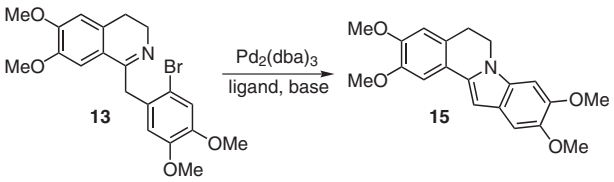
Since Nolan's study has established the accessibility of the dibenzopyrrocoline core in conventional Buchwald–Hartwig coupling, we only proved that it also works on **14** [it gave **16** in 51% yield using a $Pd(dba)_2$/SIMes catalyst system and Cs_2CO_3 in toluene], and decided to focus our attention on the palladium-catalyzed construction of the tetracyclic core starting from dihydroisoquinoline **13**. Following the optimization of the reaction conditions in this ring closure, we had two further aims in mind: i) to test the feasibility of the developed conditions in the preparation of natural product mangochinine (**5**); and ii) to study the scope and limitations of this new transformation.

In the first attempt to convert **13** to **15** (Scheme 3) we checked if the reaction worked in the absence of palladium, but the starting material remained unchanged even on prolonged heating under these conditions. The reactions, run at 80 °C, were followed by TLC and in later cases they were continued until the consumption of **13**. Increase of the temperature was found, in general, to facilitate decomposition and lead only to minor rate increase. The addition of palladium (8 mol%) to the reaction in the absence of ligands led to no conversion either. Monodentate ligands such as triphenylphosphine and tri(*o*-tolyl)phosphine (Table 1, entries 3–5), although initiated some transformation, gave only very poor conversion and no selective transformation. Switching to the bidentate dppf as ligand (entries 6–10) improved the situation considerably. Of the conditions tested, the use of Cs_2CO_3 as base and toluene as solvent gave the highest yield (entry 7, 62%). In the next series of experiments we tested some N-heterocyclic carbenes that were also used by Nolan as ligand (entries 11–17, IMes = *N*,*N*′-dimesitylimidazolium tetrafluoroborate, IPr = *N*,*N*′-bis(2′,6′-diisopropylphenyl)imidazolium tetrafluoroborate, SIPr = *N*,*N*′-bis(2′,6′-diisopropylphenyl)dihydroimidazolium tetrafluoroborate). The first experiments revealed that the IMes ligand exerts a reactivity similar to dppf, but in this case the use of *t*-BuONa as base gives superior results (entries 11, 12). Switching to the



Scheme 2 Model chemistry

sterically more demanding IPr ligand framework we observed an increased activity (entries 13, 14), a change opposite to what had been observed by Nolan in the **14** → **16** like transformation.[18] Although the 78% isolated yield achieved with this catalyst is already an acceptable result, we could further improve the efficiency of the transformation by changing to the imidazoline-based ligand SIPr (entries 15–17), which in toluene gave **15** in 85% yield. The comparison of entries 11–17 also reveals that for this transformation toluene is the best solvent amongst the ones we tried, and sodium *tert*-butoxide is the base of choice. We could also obtain the same yields when starting from the hydrochloride salt of **13**, preferable due to its increased stability and the ease of its handling and purification, only the amount of added base had to be increased to 2.4 equivalents. The activity of the NHC ligands was also manifested in the fact that the transformations in entries 11–17 reached completion faster than with dppf or other ligands.



Scheme 3 Alternate ring-closing approach involving the tautomeric enamine form

To be able to test the utility of this transformation in the preparation of mangochinine (**5**), first we had to prepare the appropriate protected dihydroisoquinoline derivative **21**. Our approach (Scheme 4.) started from homoveratronitrile (**9**), which was converted in a multistep sequence to the appropriately functionalized phenylacetic acid **7** and phenethylamine **8** derivative, which through formation of amide **20** and the Bischler–Napieralsky reaction gave **21**. The opening step of the synthesis was the selective demethylation of **9**, developed by Szántay,[23] which gave the two monomethylated isomers **17** and **18** in a 45:55 ratio. Since the separation of **17** and **18** by chromatography or distillation is tedious, we used the selective halogenation of the **17/18** mixture, of which **18** was preferentially converted to **19** on treatment with bromine at low temperature, while **17** remained intact. Both components of the reaction mixture, **17** and **19**, could be isolated in good yield by simple manipulations.

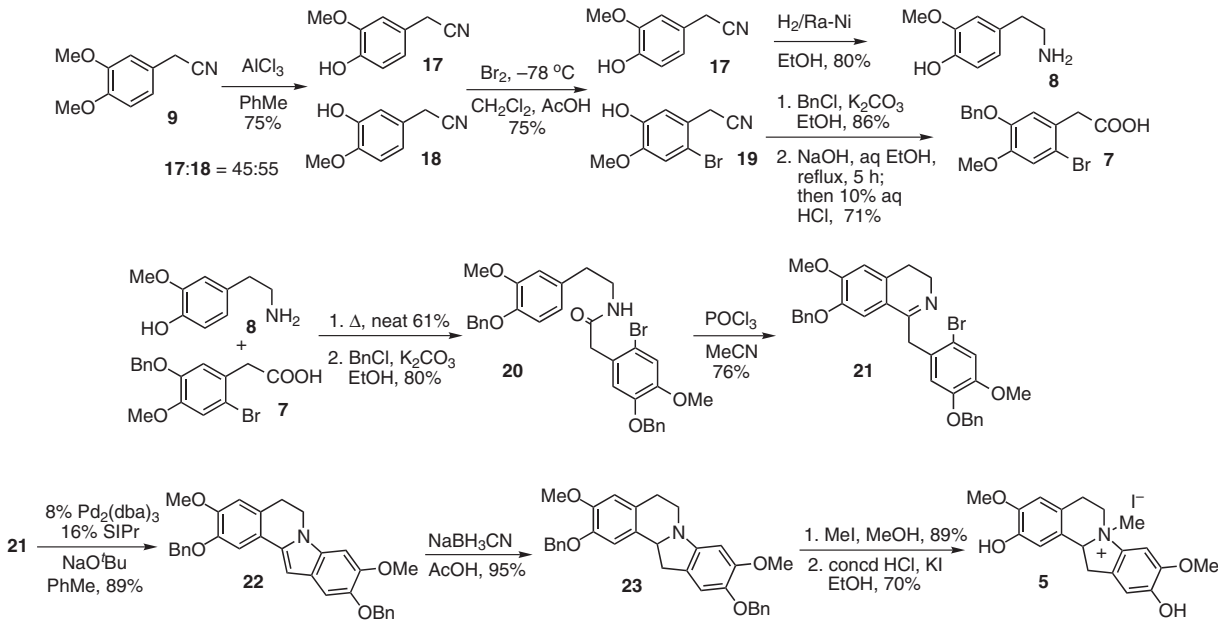
Compound **17** was reduced to **8** in good yield by conventional hydrogenation. The hydroxyl group of **19** was benzylated and the protected nitrile was hydrolyzed to the appropriate carboxylic acid **7**. Attempts at converting **7** and **8** to the desired amide through an acid chloride gave poor selectivity, since the unprotected hydroxyl group of **8** was also acylated. Its protection in the presence of the free amine was also problematic, especially since we wanted to use benzyl protection. The formation of the desired amide was finally achieved by the direct reaction of **7** and **8** in their melt. The free hydroxyl group in the amide, isolated in 61% yield, was benzylated to give **20** in good yield. We had to protect the OH group since its presence was found to result in poor yields in the subsequent Bischler–Napieralsky reaction. Following a series of test reactions we found that the optimal conditions for the ring closure included the use of phosphorous oxychloride in acetonitrile, which gave **21** in 76% yield.

Table 1 Efficiency of the Palladium-Catalyzed Conversion of **13** to **15** under Different Conditions

Entry	Ligand	Base	Solvent	Yield (%)[a]
1	–, no Pd	Cs_2CO_3	toluene	0
2	–, no Pd	*t*-BuONa	toluene	0
3	–, $Pd_2(dba)_3$	–	toluene	0
4	PPh_3	*t*-BuONa	toluene	0
5	P(*o*-tol)$_3$	*t*-BuONa	toluene	20
6	dppf	*t*-BuONa	toluene	50
7	dppf	Cs_2CO_3	toluene	62
8	dppf	*t*-BuONa	DME	40
9	dppf	Cs_2CO_3	DME	43
10	dppf	Cs_2CO_3	dioxane	45
11	IMes	Cs_2CO_3	toluene	40
12	IMes	*t*-BuONa	toluene	65
13	IPr	*t*-BuONa	DME	60
14	IPr	*t*-BuONa	toluene	78
15	SIPr	*t*-BuONa	DME	60
16	SIPr	*t*-BuONa	dioxane	63
17	SIPr	*t*-BuONa	toluene	85

[a] Isolated yields. Reactions were run in the presence of Pd [8 mol% as $Pd_2(dba)_3$], ligand (16 mol%) and base (1.4 equiv) at 80 °C until completion.

The key step of the synthesis, the palladium-catalyzed ring closure leading to the dibenzopyrrocoline frame was achieved in excellent yield, using the established conditions. Running the process in toluene at 80 °C in the presence of 8 mol% Pd in the form of $Pd_2(dba)_3$, 16 mol% SIPr and 1.4 equivalents of *t*-BuONa afforded **22** in 89% yield. The preparation of racemic mangochinine (**5**) from **22** was achieved by following literature analogies. Compound **22** was reduced by $NaBH_3CN$ in acetic acid to give **23** in a near quantitative yield. Since **23** is quite sensitive to oxidation, it was stabilized by alkylation with excess methyl iodide, which gave the desired salt in 89% yield. In the concluding step deprotection of the two hydroxyl groups led to the formation of *rac*-mangochinine (**5**) in good yield.

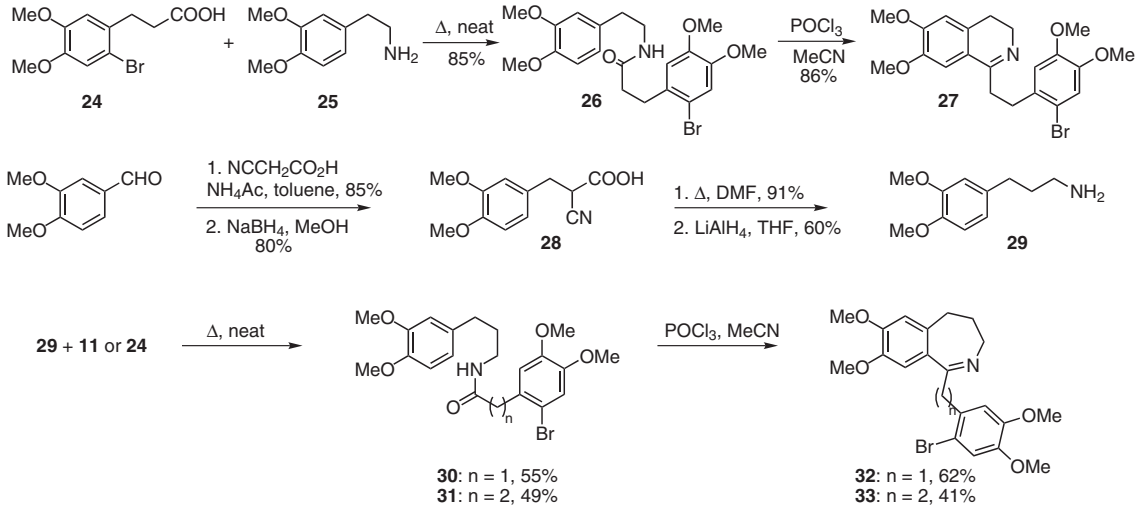


Scheme 4 Total synthesis of racemic mangochinine

Following the successful preparation of the indolo[2,1-*a*]-isoquinoline frame and its use in the synthesis of *rac*-mangochinine we wanted to study the scope of this new palladium catalyzed transformation. We hoped that extension of this strategy might open up a new synthetic route to other systems, such as the dibenzo[*a*,*f*]quinolisine **34**, indolo[2,1-*a*]-2-benzazepine **35** and quinolo[2,1-*a*]-2-benzazepine **36**. In the preparation of the ring-closed precursors we followed a strategy similar to that developed for dibenzopyrrocoline derivatives. The synthesis of intermediates and precursors is shown in Scheme 5.

The precursors to be prepared included the dihydroisoquinoline derivative **27**, and the benzazepine derivatives **32** and **33**. The preparation of **27** started from 6-bromo-3,4-dimethoxyphenylpropionic acid (**24**)[24] which was first converted to the desired amide **26** through coupling with 3,4-dimethoxyphenethylamine (**25**) in their melt. The closure of the dihydroisoquinoline ring proceeded smoothly under standard conditions to give **27** in 86% yield.

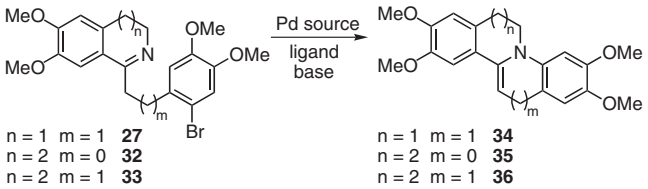
The analogous benzazepine derivatives **32** and **33** were prepared in a multistep sequence. Knoevenagel condensation of 3,4-dimethoxybenzaldehyde with cyanoacetic acid, followed by reduction gave the cyanoacid **28** in good yield, which was decarboxylated to appropriate phenylpropionitrile derivative. Reduction of the nitrile group with $LiAlH_4$ gave the desired amine **29** in acceptable yield. Compound **29** was acylated with the bromophenylalkanoic acids **11** and **24** at 180 °C, using solvent-free conditions. Although the desired amides **30** and **31** were isolated only in modest yield (55 and 49%, respectively),



Scheme 5 Preparation of starting materials for the study of the intramolecular Buchwald–Hartwig coupling through tautomeric enamines

the alternate routes utilizing the appropriate acid chlorides were less successful. The Bischler–Napieralsky-type ring closure of the amides in acetonitrile gave the appropriately substituted benzazepine derivatives **32** and **33**.

The palladium-catalyzed ring-closing reactions of **27**, **32** and **33** (Scheme 6) were carried out under inert conditions using 8 mol% Pd in the form of $Pd_2(dba)_3$, 16 mol% ligand and 1.4 equivalents of base (or 2.4 equivalents if the imine hydrochloride salt was used as starting material). Results of the ring-closure experiments are summarized in Table 2.



Scheme 6 Study of the intramolecular Buchwald–Hartwig coupling through the tautomeric enamine forms

Table 2 Efficiency of the Palladium-Catalyzed Ring-Closure/Double-Bond-Migration Process under Different Conditions

Starting material	Ligand	Base	Solvent	Yield (%)[a]
32	dppf	Cs_2CO_3	dioxane	32
32	dppf	Cs_2CO_3	DME	33
32	dppf	Cs_2CO_3	toluene	55
32	dppf	*t*-BuONa	toluene	50
32	IMes	*t*-BuONa	toluene	67
32	IPr	*t*-BuONa	DME	65
32	SIPr	*t*-BuONa	DME	68
32	SIPr	*t*-BuONa	dioxane	61
32	SIPr	*t*-BuONa	toluene	85
32	SIPr	Cs_2CO_3	toluene	40
27 or **33**	dppf	Cs_2CO_3	toluene	–[b]
27 or **33**	dppf	*t*-BuONa	toluene	–[b]
27 or **33**	IPr	*t*-BuONa	toluene	–[b]
27 or **33**	IPr	Cs_2CO_3	toluene	–[b]
27 or **33**	SIPr	*t*-BuONa	toluene	–[b]
27 or **33**	SIPr	Cs_2CO_3	DME	–[b]
27 or **33**	SIPr	Cs_2CO_3	DME	–[b]
27 or **33**	SIPr	Cs_2CO_3	toluene	–[b]
27 or **33**	SIPr	*t*-BuONa	dioxane	–[b]

[a] Isolated yields. Reactions were run in the presence of Pd [8 mol% as $Pd_2(dba)_3$], 16 mol% ligand (16 mol%) and base (1.4 equiv) at 80 °C until completion.
[b] Starting material was recovered.

As the presented data show, the ring-closing reactions of **32**, leading to the formation of the indolobenzazepine system, proceeded with varying efficiency. The results are in good agreement with those obtained for the ring closure of **13**. Dppf was in general less effective than the N-heterocyclic carbene ligands, the latter giving good yields in certain cases. The bases tested gave similar results for dppf, while for NHCs the use of sodium *tert*-butoxide gave superior results. The increase of the catalyst loading had a negligible effect on the yield, while its decrease led to diminished yields. Under the optimized conditions we were able to convert **32** to the desired tetracycle **35** in 85% yield.

Following the successful preparation of the dibenzopyrrocoline **15** and indolobenzazepine **35** systems through the Buchwald–Hartwig coupling of their enamine tautomeric forms, attempts were made at extending this methodology to transformations that incorporate the formation of a six-membered ring. Both **27** and **33** were subjected to a series of such conditions that had previously initiated ring closure. To our disappointment, we were unable to achieve any ring closure, even on prolonged heating at elevated temperatures (Table 2). We were able to recover most of the starting material from these reactions, which suggests that, in spite of the likely formation of the arylpalladium complexes, the ring closure does not take place. A probable explanation of this seemingly surprising fact might arise on the closer observation of the proposed intermediates in these transformations (Figure 2). In the course of the observed ring closure of **13** to **15** following the oxidative addition of the palladium into the carbon–bromine bond, tautomerization and intramolecular ligand exchange produces a six-membered palladacycle **37**, from which reductive elimination is expected to furnish the dibenzopyrrocoline core. The analogous transformation of **27** should proceed via the formation of a seven-membered palladacycle **38**, which is less likely due to the size of the formed ring. Another factor facilitating the formation of **37**, and not being present in **38**, is the fact that in the former case the migration of the double bond from the dihydroisoquinoline fragment to the exocyclic position results in extended conjugation.

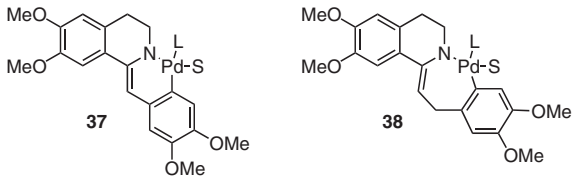


Figure 2 Proposed intermediates in the ring-closing reaction

We also tried to initiate the formation of **37** like intermediates through the directed palladation of bromine-free analogues of **27**, but these attempts remained in vain.

Summary

We studied the use of the Buchwald–Hartwig coupling in the formation of the dibenzopyrrocoline core and established that the coupling of cyclic enamines, formed in a tautomeric equilibrium, can be utilized to furnish the indolo[2,1-*a*]dihydroisoquinoline skeleton. This approach was successfully exploited in the preparation of *rac*-mangochinine. Attempts at extending this new ring-closure protocol to other systems were only partially successful. Transformations resulting in the formation of a five-membered ring worked efficiently, while the analogous closure of six-membered rings did not take place at all. This striking difference in reactivity was attributed to the different characteristics of the intermediate palladium complexes.

Unless otherwise indicated, all starting materials were obtained from commercial suppliers (Aldrich, Fisher, Merck) and were used without further purification. Analytical TLC was performed on Polygram SIL G/UV 254 pre-coated plastic TLC plates with 0.25 mm silica gel from Macherey-Nagel. Silica gel column chromatography was carried out with Flash silica gel (0.040–0.063 mm) from Merck. When using hexane–EtOAc mixtures for separation, the column was prepared by using hexane and the chromatography was carried out by increasing the EtOAc content of the eluent gradually. Melting points were determined using a Büchi melting point apparatus. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-250 spectrometer in $CDCl_3$ or DMSO-d_6. Chemical shifts (δ) are expressed in parts per million using residual solvent protons as internal standards: $CHCl_3$ (δ = 7.26 for ^{1}H, δ = 77 for ^{13}C), DMSO (δ = 2.50 for ^{1}H, δ = 39.43 for ^{13}C). Coupling constants (*J*) are reported in Hertz (Hz). Melting points were determined on a hot plate and are uncorrected. The IR spectra were obtained on a Bruker IFS-55 FTIR spectrometer.

The following compounds were prepared according to literature procedures: 2-bromo-4,5-dimethoxyphenylacetic acid (**10**),[19] 2-(3′,4′-dimethoxyphenyl)ethylamine (**11**),[25] 4-hydroxy-3-methoxyphenylacetonitrile (**17**),[23] 2-bromo-5-hydroxy-4-methoxyphenylacetonitrile (**19**)[23] 2-cyano-3-(3,4-dimethoxyphenyl)propionic acid (**28**),[26] and 3-(3′,4′-dimethoxyphenyl)propylamine (**29**).[27]

5-Benzyloxy-2-bromo-4-methoxyphenylacetic Acid (7)

Benzyl chloride (5.08 g, 0.040 mol) and K_2CO_3 (6.64 g, 0.048 mol) were added to the suspension of 2-bromo-5-hydroxy-4-methoxyphenylacetonitrile (**19**; 10.00 g, 0.040 mol) in EtOH (200 mL). The mixture was refluxed for 5 h, then the solvent was evaporated and the solid residue was triturated with CH_2Cl_2 (100 mL). The organic phase was washed with H_2O (2 × 80 mL), dried ($MgSO_4$) and removal of the solvent under reduced pressure gave an off-white solid, which was recrystallized from EtOH to yield 5-benzyloxy-2-bromo-4-methoxyphenylacetonitrile as white crystals (11.42 g, 86%); mp 94–95 °C (Lit.[28] mp 94–95 °C).

5-Benzyloxy-2-bromo-4-methoxyphenylacetonitrile

^{1}H NMR (250 MHz, $CDCl_3$ + DMSO-d_6): δ = 3.08 (s, 2 H), 3.63 (s, 3 H), 4.60 (s, 2 H), 6.50 (s, 1 H), 6.58 (s, 1 H), 6.98–6.80 (m, 5 H).

^{13}C NMR (62.5 MHz, $CDCl_3$ + DMSO-d_6): δ = 24.1, 56.3, 70.8, 112.0, 115.2, 117.8, 117.9, 127.3, 127.7, 128.0, 128.5, 136.5, 147.5, 148.9.

A mixture of 5-benzyloxy-2-bromo-4-methoxyphenylacetonitrile (16.60 g, 0.050 mol) and NaOH (8.00 g, 0.200 mol) in H_2O (40 mL) and EtOH (40 mL) was refluxed for 5 h. The mixture was allowed to cool to r.t. and was diluted with H_2O (200 mL). The solution was washed with toluene (2 × 100 mL) and the orange colored aqueous phase was acidified with 10% aq HCl (ca. 50 mL). The precipitated crystals were collected, washed with H_2O and recrystallized from EtOH to afford **7** as white crystals (12.4 g, 71%).

7

Mp 142–143 °C (Lit.[25b] mp 145 °C).

^{1}H NMR (250 MHz, $CDCl_3$ + DMSO-d_6): δ = 3.08 (s, 2 H), 3.63 (s, 3 H), 4.60 (s, 2 H), 6.50 (s, 1 H), 6.58 (s, 1 H), 6.98–6.80 (m, 5 H), 7.25–7.30 (br s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$ + DMSO-d_6): δ = 42.4, 56.2, 71.0, 115.4, 116.0, 116.7, 127.4, 127.7, 128.0, 128.5, 136.6, 147.5, 149.2, 172.2.

2-(4′-Hydroxy-3′-methoxyphenyl)ethylamine (8)

A solution of **17** (3.88 g, 0.031 mol) in 10% NH_3/EtOH (40 mL) was reduced under 10 atm H_2 pressure in the presence of Ra-Ni catalyst (5%) at 70 °C. After the uptake of H_2 had stopped, the hot suspension was filtered, and the catalyst was washed with EtOH (3 × 20 mL). The combined organic phases were concentrated to 40 mL, left to stand overnight and the precipitated white crystals were collected (3.88 g, 75%); mp 153–154 °C (Lit.[23] mp 156–158 °C).

^{1}H NMR (250 MHz, $CDCl_3$ + DMSO-d_6): δ = 1.19 (br s, 2 H), 2.56 (t, *J* = 6.3 Hz, 2 H), 2.81 (t, *J* = 6.3 Hz, 2 H), 3.70 (s, 3 H), 6.55 (dd, J_1 = 6.0 Hz, J_2 = 1.8 Hz, 1 H), 6.58 (d, *J* = 1.8 Hz, 1 H), 6.60 (d, *J* = 6.0 Hz, 1 H), 9.01 (br s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$ + DMSO-d_6): δ = 39.9, 44.0, 56.1, 111.5, 112.3, 121.0, 132.7, 143.6, 147.1.

2-(2-Bromo-4,5-dimethoxyphenyl)-*N*-(3′,4′-dimethoxyphenylethyl)acetamide (12)

2-Bromo-4,5-dimethoxyphenylacetic acid (**10**; 5.00 g, 18.2 mmol) was dissolved in $SOCl_2$ (25 mL) and refluxed for 1 h. Following the addition of toluene the excess $SOCl_2$ was removed by azeotropic distillation under reduced pressure. The resulting acid chloride was dissolved in anhyd Et_2O (50 mL) and added dropwise to a vigorously stirred mixture of **11** (3.42 g, 18.9 mmol) in Et_2O (150 mL) and 5% aq Na_2CO_3 solution (150 mL) at 0–5 °C. The mixture was allowed to warm to r.t. and stirred for an additional 6 h. The precipitated white solid was filtered and dissolved in CH_2Cl_2 (50 mL). The organic phase was washed with 10% aq NaOH solution (2 × 20 mL) and 10% aq HCl (2 × 20 mL). The organic phase was dried ($MgSO_4$), filtered and the solvent was evaporated under reduce pressure to yield white crystals (6.38 g, 80%); mp 158–159 °C (Lit.[6] mp 158–159).

IR (KBr): 3300, 1645, 1593, 1492 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.55 (t, *J* = 7.0 Hz, 2 H), 3.34 (dt, J_1 = 7.0 Hz, J_2 = 6.0 Hz, 2 H), 3.50 (s, 2 H), 3.74 (s, 3 H), 3.76 (s, 3 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 5.80–5.90 (br, 1 H), 6.58 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H), 6.62 (d, *J* = 2.0 Hz, 1 H), 6.65 (d, *J* = 8.0 Hz, 1 H), 6.78 (s, 1 H), 6.89 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 32.5, 35.1, 40.7, 56.2, 56.3, 56.5, 56.6, 111.5, 112.0, 114.1, 115.1, 115.9, 120.5, 127.1, 134.3, 147.6, 149.1, 149.2, 149.3, 170.2.

Bischler–Napieralski Ring-Closure Reaction; 1-(2′-Bromo-4′,5′-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (13); Typical Procedure

Freshly distilled $POCl_3$ (3.64 mL, 6.00 g, 39.2 mmol) was added to a solution of **13** (7.89 g, 18 mmol) in MeCN (150 mL) and the mixture was refluxed for 4 h. The excess of $POCl_3$ and the solvent were removed under reduced pressure to yield a red oil. The residue was crystallized from Et_2O to give an orange solid. Conc. NH_4OH (30 mL) was added to the filtered solid and the mixture was extracted

with CH_2Cl_2 (3 × 25 mL). The combined organic phases were washed with H_2O (20 mL), dried ($MgSO_4$), and the solvent was evaporated under reduce pressure to yield a pale-yellow oil, which crystallized to a pale-yellow solid from isopropyl ether. If necessary the product was further purified by column chromatography on silica gel using hexane–Et_2O as eluent. Pale-yellow crystals; yield: 5.74 g (76%); mp (as HCl salt) 228–230 °C (Lit.[6] mp 232 °C).

IR (KBr): 2941, 2635, 1645, 1624, 1608, 1508 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.65 (t, *J* = 8.3 Hz, 2 H), 3.66 (t, *J* = 8.3 Hz, 2 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 3.90 (s, 3 H), 3.97 (s, 2 H), 6.84 (s, 1 H), 7.01 (s, 1 H), 7.03 (s, 1 H), 7.26 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 25.6, 38.3, 41,5, 56.5, 56.6, 56.8, 56.9, 111.3, 112.5, 113.5, 114.2, 116.1, 117.4, 125.5, 134.2, 148.9, 149.7, 149.9, 156.7, 174.8.

1-(2′-Bromo-4′,5′-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (14)[13]

To a solution of **13**·HCl (0.20 g, 0.44 mmol) in MeOH (4 mL), was added $NaBH_4$ (0.017 g, 0.44 mmol) in small portions at r.t. under argon. The mixture was stirred for 7 h. After removal of the MeOH under reduced pressure, the residue was treated with aq NH_4Cl (4 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane–EtOAc as eluent to give **14** as a yellow oil (0.148 g, 73%).

^1H NMR (250 MHz, $CDCl_3$): δ = 2.80 (m, 2 H), 2.91 (m, 2 H), 3.23 (m, 2 H), 3.72 (s, 3 H), 3.78 (t, *J* = 5.7 Hz, 9 H), 4.25 (m, 1 H), 6.55 (d, *J* = 6.1 Hz, 2 H), 6.74 (s, 1 H), 6.98 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 40.3, 42.4, 55.1, 55.8, 55.9, 56.1, 56.2, 109.7, 111.7, 114.5, 114.8, 115.7, 118.8, 126.7, 129.2, 130.0, 147.2, 147.8, 148.3, 148.4.

Palladium-Catalyzed Ring Closure Reaction; 2,3,9,10-Tetramethoxy-5,6-dihydroindolo[2,1-*a*]isoquinoline (15); Typical Procedure

A Schlenk tube was charged with the cyclic imine **13** (336 mg, 0.80 mmol), *t*-BuONa (108 mg, 1.12 mmol), ligand (0.128 mmol, 16 mol%), $Pd_2(dba)_3$ (29 mg, 8 mol% Pd), and flushed with argon. Following the addition of anhyd toluene (4 mL) via syringe the mixture was heated under argon at 80 °C until consumption of the starting material. The solution was allowed to cool to r.t. and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (8 mL) and the organic layer was washed with H_2O (2 × 5 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure to give an off-white solid, which was purified by column chromatography on silica gel using hexane–EtOAc as eluent. Pale-green crystals; yield: 230 mg (85%); mp 205–206 °C (Lit.[15] mp 207–208 °C).

IR (KBr): 1623, 1609, 1547, 1503 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 3.14 (t, *J* = 6.9 Hz, 2 H), 3.94 (s, 3 H), 3.96 (s, 3 H), 3.98 (s, 3 H), 3.99 (s, 3 H), 4.19 (t, *J* = 6.9 Hz, 2 H), 6.67 (s, 1 H), 6.78 (s, 1 H), 6.83 (s, 1 H), 7.10 (s, 1 H), 7.20 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 29.1, 40.7, 55.9, 56.1, 56.5, 56.6, 92.4, 98.4, 102.3, 111.8, 112.3, 120.6, 125.9, 130.4, 134.0, 140.2, 145.2, 146.8, 147.7, 148.8.

2,3,9,10-Tetramethoxy-5,6,12,12a-tetrahydroindolo[2,1-*a*]isoquinoline (16)

A Schlenk tube was charged with **14** (0.100 g, 0.23 mmol), Cs_2CO_3 (0.149 g, 0.46 mmol), SIPr (2.1 mg, 2 mol%), $Pd_2(dba)_3$, (4.2 mg, 2 mol% Pd) and flushed with argon. Anhyd DMA (2 mL) was added via syringe and the mixture was heated at 80 °C under argon until consumption of the starting material. The solution was allowed to cool to r.t. and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (4 mL) and the organic layer was washed with H_2O (2 × 5 mL), and dried ($MgSO_4$). Following the removal of the solvent under reduced pressure the mixture was purified by column chromatography on silica gel using hexane–EtOAc as eluent to give **16** as white crystals (40 mg, 51%); mp 104–105 °C (Lit.[11] mp 105–107 °C).

^1H NMR (250 MHz, $CDCl_3$): δ = 2.36 (m, 1 H), 2.95 (m, 2 H), 3.24 (m, 1 H), 3.40 (m, 1 H), 3.78 (m, 13 H) 4.74 (d, *J* = 7.5 Hz, 1 H), 6.24 (s, 1 H), 6.40 (s, 1 H), 6.63 (m, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 40.7, 43.5, 55.9, 56.1, 56.5, 56.9, 98.4, 110.7, 112.3, 114.5, 114.8, 115.7, 118.8, 126.7, 129.2, 130.0, 146.2, 146.8, 147.3, 147.6.

2-(5-Benzyloxy-2-bromo-4-methoxyphenyl)-*N*-(4′-benzyloxy-3′-methoxyphenylethyl)acetamide (20)

A mixture of **7** (7.02 g, 0.02 mol) and **8** (3.34 g, 0.02 mol) was heated to 180 °C and the melt was stirred at the same temperature for 3 h. After cooling to r.t. and dilution with CH_2Cl_2 (50 mL), the organic layer was washed successively with 10% aq NaOH (2 × 15 mL), 10% aq HCl (2 × 15 mL) and H_2O (15 mL). The organic phase was dried ($MgSO_4$), and the solvent was removed under reduced pressure to give *N*-(4′-benzyloxy-3′-methoxyphenylethyl)-2-(2-bromo-5-hydroxy-4-methoxyphenyl)acetamide as an off-white solid, which was recrystallized from a mixture of MeOH–Et_2O to give white crystals (10.02 g, 61%).

N-(4′-Benzyloxy-3′-methoxyphenylethyl)-2-(2-bromo-5-hydroxy-4-methoxyphenyl)acetamide

Mp 143–144 °C.

IR (KBr): 3293, 1620, 1526, 1507, 1262, 1220 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.57 (t, *J* = 7.0 Hz, 2 H), 3.33 (dt, J_1 = 7.0 Hz, J_2 = 6.0 Hz, 2 H), 3.46 (s, 2 H), 3.77 (s, 3 H), 3.80 (s, 3 H), 5.01 (s, 2 H), 5.27–5.35 (br, 1 H), 5.52–5.65 (br, 1 H), 6.42 (dd, J_1 = 7.9 Hz, J_2 = 1.7 Hz, 1 H), 6.53 (d, *J* = 1.7 Hz, 1 H), 6.69 (d, *J* = 7.9 Hz, 1 H), 6.73 (s, 1 H), 6.93 (s, 1 H), 7.22–7.36 (m, 5 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 34.0, 39.8, 42.5, 54.9, 55.2, 68.8, 70.1, 110.0, 113.3, 114.4, 115.0, 115.4, 120.3, 125.3, 126.4, 127.1, 127.6, 129.3, 135.3, 143.2, 145.6, 146.7, 148.7, 168.8.

Anal. Calcd for $C_{25}H_{26}BrNO_5$: C, 60.01; H, 5.24; N, 2.80. Found: C, 59.85; H, 5.20; N, 2.70.

Benzyl chloride (1.27 g, 0.010 mol) and K_2CO_3 (1.66 g, 0.012 mol) were added to a suspension of *N*-(4′-benzyloxy-3′-methoxyphenylethyl)-2-(2-bromo-5-hydroxy-4-methoxyphenyl)acetamide (5.00 g, 0.010 mol) in EtOH (50 mL). The mixture was refluxed for 6 h, then the solvent was evaporated under reduced pressure and the solid residue was triturated with CH_2Cl_2 (30 mL). The organic phase was washed with H_2O (2 × 30 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure to give a yellow solid, which was triturated with Et_2O to yield an off-white solid. The product was recrystallized from EtOH to yield **20** as white crystals (4.72 g, 80%).

20

Mp 130–131 °C.

IR (KBr): 3336, 2934, 1643, 1506, 1259, 1029, 697 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 2.57 (t, *J* = 7.1 Hz, 2 H), 3.35 (dt, J_1 = 7.1 Hz, J_2 = 5.8 Hz, 2 H), 3.46 (s, 2 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 5.01 (s, 2 H), 5.03 (s, 2 H), 5.27–5.34 (br, 1 H), 6.42 (dd, J_1 = 8.0 Hz, J_2 = 1.9 Hz, 1 H), 6.65 (d, *J* = 8.0 Hz, 1 H), 6.57 (d, *J* = 1.9 Hz, 1 H), 7.22–7.37 (m, 10 H), 6.92 (s, 1 H), 6.74 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 35.4, 41.0, 43.9, 56.3, 56.6, 71.5, 112.7, 114.5, 115.8, 116.4, 116.7, 120.9, 126.8, 127.6, 127.8, 128.2, 128.5, 128.9, 129.0, 132.0, 136.7, 137.6, 147.2, 148.1, 150.0, 170.1.

Anal. Calcd for $C_{32}H_{32}BrNO_5$: C, 65.09; H, 5.46; N, 2.37; Found: C, 64.89; H, 5.35; N, 2.40.

7-Benzyloxy-1-(5′-benzyloxy-2′-bromo-4′-methoxybenzyl)-6-methoxy-3,4-dihydroisoquinoline (21)

The typical procedure described for the synthesis of **13** was applied to **20** (4.0 g, 6.78 mmol). The crude product was recrystallized from hexane–EtOAc to give **21** as white crystals (2.95 g, 76%); mp 105–106 °C.

IR (KBr): 1622, 1602, 1569, 1509, 1507, 1504, 1464 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.52 (t, *J* = 7.6 Hz, 2 H), 3.64 (t, *J* = 7.6 Hz, 2 H), 3.84 (s, 3 H), 3.89 (s, 3 H), 3,97 (s, 2 H), 5.00 (s, 2 H), 5.04 (s, 2 H), 6.64 (s, 1 H), 6.75 (s, 1 H), 6.94 (s, 1 H), 7.03 (s, 1 H), 7.26–7.35 (m, 10 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 26.1, 42.5, 47.7, 56.4, 56.6, 71.0, 71.5, 110.9, 112.2, 115.0, 115.2, 116.1, 121.4, 121.6, 127.8, 128.1, 128.3, 128.8, 128.9, 129.8, 132.3, 137.0, 137.2, 146.8, 147.9, 149.2, 151.8, 165.6.

Anal. Calcd for $C_{32}H_{30}BrNO_4$: C, 67.14; H, 5.28; N, 2.45. Found: C, 66.99; H, 5.39; N, 2.38.

2,10-Di(benzyloxy)-3,9-dimethoxy-5,6-dihydroindolo[2,1-*a*]isoquinoline (22)

A Schlenk tube was charged with **21** (2.00 mmol), *t*-BuONa (270 mg 2.80 mmol), ligand SIPr (136 mg, 0.32 mmol, 16 mol%), $Pd_2(dba)_3$ (72 mg, 8 mol% Pd) and flushed with argon. Anhyd toluene (10 mL) was added via syringe and the mixture was heated at 80 °C under argon for 6 h. The solution was allowed to cool to r.t. and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), the organic layer was washed with H_2O (2 × 10 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give a yellow solid, which was purified by column chromatography on silica gel using hexane–EtOAc as eluent to give **22** as off-white crystals (884 mg, 89%); mp 117–118 °C.

IR (KBr): 1608, 1547, 1498, 1481, 1348, 1250, 1215, 1121 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.10 (t, *J* = 6.5 Hz, 2 H), 3.92 (s, 3 H), 3.97 (s, 3 H), 4.14 (t, *J* = 6.5 Hz, 2 H), 5.20 (s, 2 H), 5.21 (s, 2 H), 6.49 (s, 1 H), 6.76 (s, 1 H), 6.82 (s, 1 H), 7.09 (s, 1 H), 7.20 (s, 1 H), 7.52–7.31 (m, 10 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 29.2, 40.8, 56.9, 56.5, 71.7, 72.4, 93.3, 95.2, 106.2, 110.6, 112.1, 122.0, 122.3, 125.1, 127.8, 127.8, 128.0, 128.4, 128.9, 129.0, 132.0, 135.0, 137.5, 138.2, 144.5, 147.8, 147.9, 149.3.

Anal. Calcd for $C_{32}H_{29}NO_4$: C, 78.19; H, 5.95; N, 2.85. Found: C, 78.33; H, 6.07; N, 2.71.

2,10-Dibenzyloxy-3,9-dimethoxy-5,6,12,12a-tetrahydroindolo-[2,1-*a*]isoquinoline (23)

$NaBH_3CN$ (315 mg, 5 mmol) was added in small portions at 0 °C to a solution of **22** (490 mg, 1 mmol) in AcOH (4 mL). The mixture was stirred for 1 h at r.t., then it was cooled to 0 °C, and H_2O (4 mL) was added dropwise to the mixture. After the gas evolution had stopped, the mixture was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic phases were washed with aq 2 M NaOH solution (2 × 15 mL), H_2O (10 mL), and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a yellow solid, which was triturated with Et_2O. The product was filtered and recrystallized from hexane–EtOAc to give **23** as white crystals (568 mg, 95%); mp 163–165 °C.

IR (KBr): 1606, 1570, 1508, 1348 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.04–2.84 (m, 2 H), 3.30–3.15 (m, 2 H), 3.61–3.52 (m, 1 H), 3.72–3.66 (m, 1 H), 3.74 (s, 3 H), 3.78 (s, 3 H), 4.67–4.64 (m, 1 H), 4.90 (s, 2 H), 5.04 (s, 2 H), 6.21 (s, 1 H), 6.43 (s, 1 H), 6.57 (s, l H), 6.60 (s, 1 H), 7.44–7.23 (m, 10 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 32.0, 37.2, 43.1, 56.4, 57.0, 63.3, 95.1, 71.9, 71.8, 112.6, 112.8, 114.9, 120.9, 127.8, 127.8, 128.1, 128.2, 128.7, 128.9, 131.4, 137.6, 138.5, 127.9, 141.6, 145.9, 147.2, 148.7, 150.6.

Anal. Calcd for $C_{32}H_{31}NO_4$: C, 77.87; H, 6.33; N, 2.84. Found: C, 78.01; H, 6.52; N, 2.50.

2,10-Dihydroxy-3,9-dimethoxy-7-methyl-5,6,12,12a-tetrahydro-indolo[2,1-*a*]isoquinolinium Iodide (5, Mangochinine Iodide)

MeI (2 mL, 4.56 g, 32 mmol) was added to a solution of **23** (394 mg, 0.80 mmol) in MeOH (4 mL). Upon standing for 1 day 2,10-di(benzyloxy)-3,9-dimethoxy-7-methyl-5,6,12,12a-tetrahydroindolo[2,1-*a*]isoquinolinium iodide crystallized as white needles. The product was recrystallized from H_2O–EtOH to yield gray-white crystals (477 mg, 94%).

2,10-Di(benzyloxy)-3,9-dimethoxy-7-methyl-5,6,12,12a-tetrahydroindolo[2,1-*a*]isoquinolinium Iodide

Mp 240–242 °C.

IR (KBr): 1620, 1545, 1507, 1484, 1447, 1351, 1253 cm^{-1}

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.82–2.89 (m, 1 H), 3.04–3.09 (m, 1 H), 3.10–3.15 (m, 1 H), 3.45 (s, 3 H), 3.52–3.55 (m, 1 H), 3.56–3.60 (m, 1 H), 3.70 (s, 3 H), 3.80 (s, 3 H), 3.80–3.85 (m, 1 H), 5.02 (s, 2 H), 5.04 (s, 2 H), 5.25 (m, 1 H), 6.85 (s,1 H), 7.05 (s, 1 H), 7.15 (s, 1 H), 7.28–7.37 (m, 10 H), 7.53 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 28.3, 35.2, 49.8, 56.0, 56.3, 57.1, 70.4, 71.1, 74.2, 105.2, 109.4, 111.9, 112.6, 121.4, 124.9, 128.1, 128.2, 128.3, 128.7, 128.8, 128.9, 131.7, 134.5, 137.0, 143.8, 147.2, 147.6, 148.7, 150.6.

Anal. Calcd for $C_{33}H_{34}INO_4$: C, 62.37; H, 5.39; N, 2.20. Found: C, 62.21; H, 5.35; N, 2.20.

5

Concd HCl (5 mL) was added to a suspension of 2,10-di(benzyloxy)-3,9-dimethoxy-7-methyl-5,6,12,12a-tetrahydroindolo[2,1-*a*]-isoquinolinium iodide (317.5 mg, 0.5 mmol) in benzene (3 mL) and the mixture was refluxed for 3 h. The mixture was allowed to cool to r.t. and the precipitated crystals were filtered. The crystals were taken up in 95% EtOH (5 mL), and KI (150 mg, 0.90 mmol) was added. After the mixture was warmed to 75 °C, the solution was filtered and the filtrate was evaporated to dryness. Recrystallization from EtOH afforded **5** as white solid (168 mg, 75%); mp 262–263 °C.

IR (KBr): 3200, 1607, 1510, 1464, 1225, 1020 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.75–2.83 (m, 1 H), 2.93–3.03 (m, 1 H), 3.07–3.13 (m, 1 H), 3.45 (s, 3 H), 3.52–3.56 (m, 1 H), 3.56–3.59 (m, 1 H), 3.64 (s, 3 H), 3.72 (s, 3 H), 3.75–3.82 (m, 1 H), 5.17 (dd, J_1 = 7.8 Hz, J_2 = 9.6 Hz, 1 H), 6.60 (s,1 H), 6.74 (s, 1 H), 6.72 (s, 1 H), 7.43 (s, 1 H), 9.17 (s, 1 H), 9.72 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 23.5, 35.9, 49.3, 55.7, 56.5, 57.7, 74.1, 102.1, 111.7, 111.8, 113.1, 119.6, 122.3, 124.5, 137.7, 146.0, 147.6, 148.2, 148.8.

Anal. Calcd for $C_{19}H_{22}INO_4$: C, 50.12; H, 4.87; N, 3.08. Found: C, 49.89; H, 4.68; N, 3.05.

3-(2′-Bromo-4′,5′-dimethoxyphenyl)propionic Acid (24)

Br_2 (3.48 g, 21.8 mmol) was added slowly to a solution of 3-(4′,5′-dimethoxyphenyl)propionic acid (4.58 g, 21.8 mmol) in glacial

AcOH (45 mL) at 0 °C. After the addition was complete, the mixture was stirred at r.t. for 3 h. The mixture was poured onto crushed ice to give white crystals. The precipitated product was filtered, washed with H_2O and dried (6.90 g, 80%); mp 119–121 °C (Lit.[29] mp 120–123 °C).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.67 (t, *J* = 7.8 Hz, 2 H), 2.99 (t, *J* = 7.4 Hz, 2 H), 3.82 (s, 3 H), 3.84 (s, 3 H), 6.77 (s, 1 H), 6.99 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 30.8, 34.1, 56.0, 56.1, 113.1, 113.9, 115.5, 131.2, 148.2, 148.3, 179.0.

3-(2′-Bromo-4′,5′-dimethoxyphenyl)-*N*-[2-(3′,4′-dimethoxyphenyl)ethyl]propionamide (26)[24]

The same procedure was followed as in the opening step in the preparation of **20** starting from 3,4-dimethoxyphenethylamine (**25**; 3.42 g, 18.2 mmol) and 3-(2′-bromo-4′,5′-dimethoxyphenyl)propionic acid (**24**; 5.46 g, 18.2 mmol). The crude product was recrystallized from EtOH to yield **26** as white crystals (7.00 g, 85%); mp 123–125 °C (Lit.[24] mp 123–125 °C).

IR (KBr): 3303, 2936, 2833, 1634, 1512 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.45 (t, *J* = 7.5 Hz, 2 H), 2.60 (t, *J* = 7.0 Hz, 2 H), 2.99 (t, *J* = 7.5 Hz, 2 H), 3.36 (dt, J_1 = 7.0 Hz, J_2 = 6.0 Hz, 2 H), 3.74 (s, 3 H), 3.76 (s, 3 H), 3.78 (s, 3 H), 3.81 (s, 3 H), 5.84–5.94 (br, 1 H), 6.57 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H), 6.63 (d, *J* = 2.0 Hz, 1 H), 6.74 (d, *J* = 8.0 Hz, 1 H), 6.90 (s, 1 H), 7.20 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 27.6, 35.0, 37,8, 40.7, 56.2, 56.3, 56.4, 56.5, 111.6, 111.9, 113.7, 114.0, 115.8, 120.4, 131.8, 134.3, 147.6, 148.5, 148.8, 149.2, 172.2.

1-[2-(2′-Bromo-4′,5′-dimethoxyphenyl)ethyl]-6,7-dimethoxy-3,4-dihydroisoquinoline (27)

Prepared according to the typical procedure described for the preparation of **13**. Starting from **26** (8.14 g, 18 mmol) **27** was obtained as pale-yellow crystals (6.72 g, 86%); mp 94–95 °C (Lit.[24] mp 95–96 °C).

IR (KBr): 3010, 2970, 2910, 2772, 1642, 1605 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.98 (t, *J* = 8.0 Hz, 2 H), 3.07 (t, *J* = 8.0 Hz, 2 H), 3.36–3.44 (m, 2 H), 3.48 (t, *J* = 8.0 Hz, 2 H), 3.72 (s, 3 H), 3.73 (s, 3 H), 3.80 (s, 3 H), 3.90 (s, 3 H), 6.78 (s, 1 H), 6.82 (s, 1 H), 7.01 (s, 1 H), 7.14 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 29.3, 35.9, 41.9, 45.7, 55.7, 55.8, 56.1, 56.2, 113.4, 113.6, 114.6, 115.7, 115.8, 121.3, 125.2, 136.9, 147.4, 148.5, 149.2, 153.4, 164.8.

2-(2′-Bromo-4′,5′-dimethoxyphenyl)-*N*-[3-(3′,4′-dimethoxyphenyl)propyl]acetamide (30)

The same procedure was followed as the opening step in the preparation of **20**. Starting from 3-(3′,4′-dimethoxyphenyl)propylamine (**29**; 3.91 g, 0.02 mol) and 3-(2′-bromo-4′,5′-dimethoxyphenyl)propionic acid (**24**; 6.00 g, 0.02 mol) white crystals were obtained (4.97 g, 55%); mp 127–129 °C (Lit.[13] mp 128–130 °C).

IR (KBr): 3281, 3086, 2940, 2836, 1646, 1559 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.66 (m, 2 H), 2.47 (t, *J* = 7.9 Hz, 2 H), 3.36 (dt, J_1 = 7.0 Hz, J_2 = 6.0 Hz, 2 H), 3.54 (s, 2 H), 3.74 (s, 3 H), 3.76, (s, 3 H), 3.78, (s, 3 H), 3.81 (s, 3 H), 5.84–5.94 (br, 1 H), 6.57 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H), 6.60 (d, *J* = 2.0 Hz, 1 H), 6.74 (d, *J* = 8.0 Hz, 1 H), 6.90 (s, 1 H), 7.20 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 31.7, 33.0, 39.5, 44.1, 56.2, 56.3, 56.5, 56.6, 111.5, 111.9, 114.1, 115.1, 115.9, 120.5, 127.07, 134.3, 147.6, 149.1, 149.2, 149.3, 170.2.

3-(2′-Bromo-4′,5′-dimethoxyphenyl)-*N*-[3-(3′,4′-dimethoxyphenyl)propyl]propionamide (31)

The same procedure was followed as the opening step in the preparation of **20**. Starting from 3-(3′,4′-dimethoxyphenyl)propylamine (**29**; 3.91 g, 0.02 mol) and 2-bromo-4,5-dimethoxyphenylacetic acid (**11**; 5.50 g, 0.02 mol), white crystals were obtained (4.57 g, 49%); mp 107–109 °C (Lit.[14] mp 108–110 °C).

IR (KBr): 3279, 3080, 2939, 2836, 1646, 1510 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.68 (m, 2 H), 2.34 (t, *J* = 7.3 Hz, 2 H), 2.45 (t, *J* = 7.9 Hz, 2 H), 2.92 (t, *J* = 7.9 Hz, 2 H), 3.17 (dt, J_1 = 7.4 Hz, J_2 = 6.3 Hz, 2 H) 3.74 (s, 3 H), 3.75 (s, 3 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 5.37–5.48 (br, 1 H), 6.59 (dd, J_1 = 7.9 Hz, J_2 = 2.0 Hz, 1 H), 6.62 (d, *J* = 2.0 Hz, 1 H), 6.75 (d, *J* = 7.9 Hz, 1 H), 6.90 (s, 1 H), 7.20 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 31.7, 32.3, 33.1, 37.3, 39.6, 56.2, 56.3, 56.4, 56.5, 111.6, 111.9, 113.7, 114.1, 115.8, 120.4, 132.4, 134.3, 147.6, 148.4, 148.7, 149.2, 172.2.

1-(2′-Bromo-4′,5′-dimethoxybenzyl)-7,8-dimethoxy-4,5-dihydro-3*H*-benzo[*c*]azepine (32)

Prepared according to the typical procedure described for the preparation of **13**. Starting from **30** (8.14 g, 18 mmol), the product **32** was obtained as pale-yellow crystals (4.84 g, 62%); mp (as HCl salt) 182–184 °C (Lit.[13] mp 180–182 °C).

IR (KBr): 2952, 2941, 2858, 2834, 2635, 1638, 1602 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.26 –2.30 (m, 2 H), 2.44–2.58 (m, 4 H), 3.76 (dt, J_1 = 6.6 Hz, J_2 = 3.0 Hz, 2 H), 3.74 (s, 2 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 6.69 (s, 1 H), 6.77 (s, 1 H), 7.21 (s, 1 H), 7.27 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 29.3, 29.4, 42.1, 45.8, 55.5, 55.6, 55.6, 55.7, 113.5, 114.7, 115.7, 121.1, 124.9, 125.5, 128.4, 129.1, 137.0, 147.5, 148.5, 149.3, 153.5.

1-[2-(2′-Bromo-4′,5′-dimethoxyphenyl)ethyl]-7,8-dimethoxy-4,5-dihydro-3*H*-benzo[*c*]azepine (33)

Prepared according to the typical procedure described for the preparation of **13**. Starting from **31** (8.39 g, 18 mmol), the product **33** was obtained as pale-yellow crystals (3.31 g, 41%); mp (as HCl salt) 175–176 °C (Lit.[14] mp 181 °C).

IR (KBr): 2930, 2923, 2833, 2625, 1640, 1600 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.34 (m, 4 H), 2.82 (t, *J* = 7.9 Hz, 2 H), 3.40 (m, 2 H), 3.59 (t, *J* = 8.1 Hz, 2 H), 3.78 (s, 3 H), 3.80 (s, 3 H), 3.84 (s, 3 H), 3.93 (s, 3 H), 6.31 (s, 1 H), 6.69 (s, 1 H), 6.79 (s, 1 H), 6.89 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 27.9, 29.1, 34.8, 35.0, 44.6, 55.4, 55.7, 55.8, 55.9, 95.8, 110.9, 112.2, 119.1, 121.1, 121.2, 133.2, 136.2, 147.7, 153.4, 156.5, 157.3, 186.5.

2,3,10,11-Tetramethoxy-6,7-dihydro-5*H*-benz[3,4]azepino-[1,2-*a*]indole (35)

Prepared by the typical procedure described for the preparation of **15**. Starting from **32** (363 mg, 0.8 mmol), the product **35** was obtained as white crystals (240 mg, 85%); mp 158–160 °C.

IR (KBr): 3093, 2997, 2932, 2834, 1717 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.35–2.23 (m, 2 H), 2.67 (t, *J* = 6.6 Hz, 2 H), 3.93 (s, 3 H), 3.94 (s, 3 H), 3.96 (s, 3 H), 3.97 (s, 3 H), 4.03 (t, *J* = 6.5 Hz, 2 H), 6.48 (s, 1 H), 6.80 (s, 1 H), 6.84 (s, 1 H), 7.06 (s, 1 H), 7.11 (s, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 30.7, 31.1, 41.2, 56.0, 56.1, 56.3, 56.4, 92.5, 98.3, 102.3, 111.8, 112.7, 120.7, 125.9, 130.4, 134.2, 140.5, 144.9, 146.7, 147.7, 148.6.

Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.39; H, 6.48; N, 3.80.

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