EurJOC
European Journal of Organic Chemistry

Research Article
doi.org/10.1002/ejoc.202200315

Chemistry Europe
European Chemical Societies Publishing

www.eurjoc.org

VIP *Very Important Paper*

Special Collection

Asymmetric Total Synthesis of All Rugulovasine Stereoisomers and Preliminary Evaluation of Their Biological Properties

Francesca Bartoccini,[a] Alessio Regni,[a] Michele Retini,[a] and Giovanni Piersanti*[a]

Dedicated to Professor Cesare Gennari on the occasion of his 70th birthday-

A unified enantioselective synthesis and the biological evaluation of all rugulovasine stereoisomers are reported. The syntheses are centered on the divergent and stereochemical modular combination of each enantiomer of 4-amino Uhle's ketone and a methacrylate derivative to build the unsaturated oxaspirolactone moiety by the Dreiding-Schmidt reaction, followed by Fukuyama alkylation to afford the required *N*-methyl secondary amine in excellent yield. The modularity of this divergent approach, the diastereoselectivities of the reactions, and the late-stage site-selective methylation permit the rapid asymmetric syntheses of all rugulovasine stereoisomers, including the first total syntheses of optically pure (+)- and (−)-rugulovasine B and their trideuteromethylated derivatives. All enantiopure stereoisomers of rugulovasine were tested for their binding affinities to dopamine, serotonin, and adrenergic neuroreceptors, revealing their preferred selectivity for the serotonin 1 A receptor.

Introduction

Clavine alkaloids are a group of indole derivatives biosynthetically obtained from L-tryptophan.[1] They are the simplest group of ergot alkaloids produced by several families of fungi in the early steps or as side products of the ergot alkaloid biosynthetic pathway, which ultimately produces lysergic acid and amide derivatives. Only limited analytical, biological, and toxicological studies have been performed on naturally occurring clavine alkaloids, likely due to insufficient material from synthetic efforts.[2] Therefore, the efficient chemical synthesis of natural clavines would provide an exciting platform to conduct fundamental research in organic and medicinal chemistry.[3] Clavine alkaloids can be roughly classified into three subclasses based on their structures and biosynthetic origins: tetracyclic, tricyclic, or rearranged.[1a] The latter subclass is more variable with a different connectivity compared to the classic tricyclic and tetracyclic structures, for example, the tricyclic clavicipitic acid azepinoindole,[4] the fused pentacyclic clavine alkaloids including a cyclopropane ring, called cycloclavines,[5] and the tetracyclic clavine alkaloids containing a spirocyclic butyrolactone such as diastereomeric rugulovasine A and B.[6]

While the precise biosynthetic mechanism for the formation of rugulovasines A (**1 a**) and B (**1 b**)[7] as well as their biological activities are largely understudied,[8] they have drawn significant attention by synthetic chemists since the 1980 s[9] because they possess the following characteristics: a) a 3,4-annulated indole structure decorated with a unique, among the ergot alkaloids, unsaturated lactone moiety in a spirocyclic subunit; b) two vicinal stereocenters that can exist as pairs of enantiomers and diastereomers (two enantiomers of rugulovasine A and two enantiomers of rugulovasine B, Figure 1); c) asymmetry, but different from most natural products, including clavines and ergot alkaloids that are commonly isolated as single enantiomers, rugulovasines A and B have been isolated as pairs of naturally occurring diastereomers in a racemic form; and d) aptitude for racemization and interconversion upon heating in

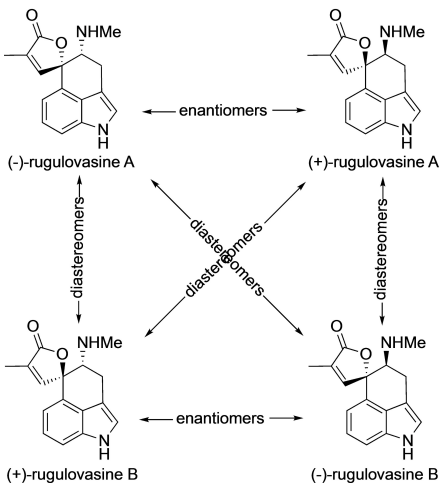


Figure 1. Configurational diversity of rugulovasines.

[a] *Dr. F. Bartoccini, Dr. A. Regni, Dr. M. Retini, Prof. G. Piersanti*
Department of Biomolecular Sciences, University of Urbino Carlo Bo
Piazza Rinascimento 6, 61029 Urbino, PU, Italy
E-mail: giovanni.piersanti@uniurb.it
https://sites.google.com/uniurb.it/giovannipiersanti

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202200315

Part of the "Cesare Gennari's 70th Birthday" Special Collection.

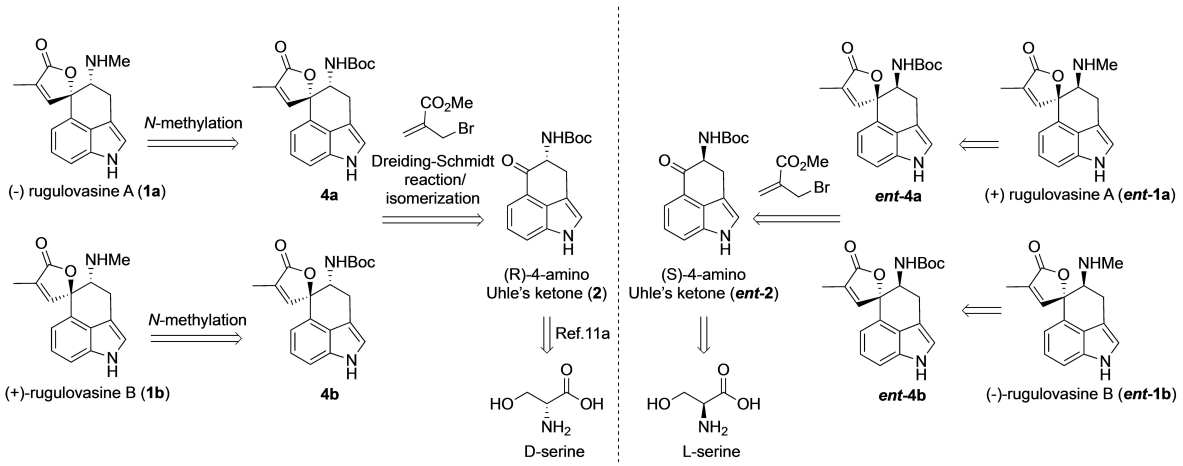
polar solvents via an unusual intramolecular reverse-vinylogous Mannich reaction through a transiently formed achiral intermediate.[9a] It has even been speculated that racemization and/or the presence of one of the two diastereomers could be an artefact of the isolation procedure.[9b] All of these structurally and stereochemically intriguing features has prompted research efforts directed toward their innovative total synthesis, culminating in ingenious solutions, both in terms of synthetic methodology and synthetic strategy, for the preparation of racemic[9a,c–e] as well as optically pure rugulovasine A.[9b] However, their therapeutic potential remains unexplored.

Results and Discussion

Our group has had a standing interest in the divergent synthesis[10] of tryptophan-based derivatives of natural products utilizing serine as a starting material.[11] Serine is of particular interest to us because of its availability in either enantiomeric form and its highly modifiable functional groups, which allow for rapid elaboration. The syntheses disclosed herein are complementary to previous approaches to rugulovasines. Specifically, we began with a cyclic "chiral pool" compound (obtained from the elaboration of L-serine or D-serine), which obviated the need for an enantiomeric[9a,c–e] or diastereomeric resolution,[9b] thus presenting a unique opportunity for divergence that culminated in the synthesis of both enantiomers of rugulovasine B in contrast to the products that had been previously achieved. Now, we report the realization of this strategy for the total synthesis of all four stereoisomers of rugulovasine and their preliminary biological evaluation on several key central nervous system (CNS) receptors.

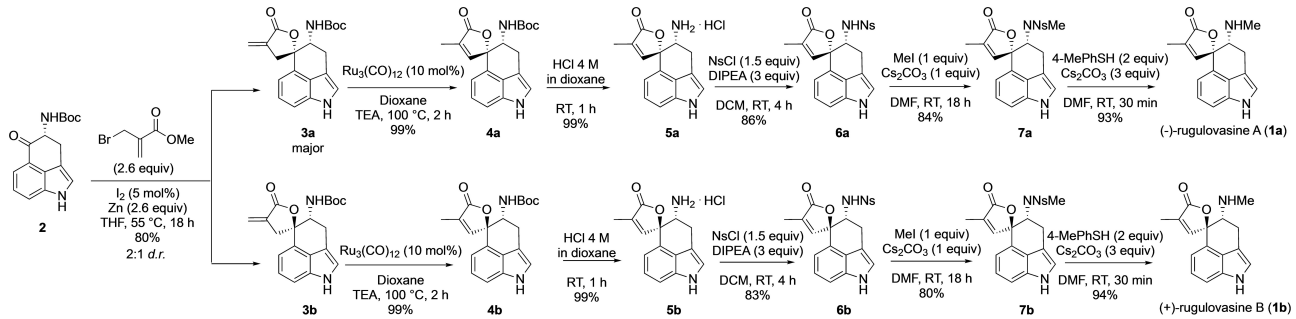
The retrosynthetic analysis of all stereoisomers of rugulovasine is shown in Scheme 1. We envisioned that rugulovasines (**1a**,**b** and ***ent*-1a**,**b**) could be accessed via mono-*N*-methylation of compounds **4a**,**b** and ***ent*-4a**,**b** either by reduction or by methylation of the *N*-Boc (or surrogates)-protected amino group. Regardless of the methodology, both the corresponding *N*-methylated and *N*-trideuteromethylated amine derivatives would be of considerable value, given the importance and applications of stable isotopically labeled compounds in the life sciences.[12] We sought a diastereoselective (confidently low), albeit highly enantioretentive, Dreiding-Schmidt reaction[13] between enantiopure α-amino ketone derivative **2** or ***ent*-2** and methyl 2-(bromomethyl)acrylate to introduce the remaining four carbons to the crucial oxaspirolactone ring. The fundamental homochiral *N*-Boc tricyclic Uhle's ketones[14] **2** and ***ent*-2** are accessible through a known four-step sequence from inexpensive and commercially available L- and D-serine, respectively, as reported by us recently.[11a]

The synthesis commenced with the Dreiding-Schmidt reaction of ketone **2**, derived from D-serine (Scheme 2).[11a] Upon the treatment of ketone **2** with the metallozinc reagent derived from methyl 2-(bromomethyl)acrylate and zinc metal, the Dreiding-Schmidt reaction proceeded smoothly to give the desired product **3a**,**b** in 80% yield with a 2:1 *cis*:*trans* diastereoselectivity (ideally 1:1 in this case) at the spirocyclic center; the two diastereomers were separated by silica gel chromatography. The preferred *cis* diastereomer obtained was not unexpected. In fact, the stereochemistry of the spirocyclic carbon center is controlled by the vicinal stereogenic center, with the nucleophile attacking the carbonyl group preferentially from the side of the smallest substituent (hydrogen), to produce the dominant *cis* isomer **3a** with the carboxylate group oriented on the same face as NHBoc, as opposed to the favored equatorial/axial approach of the nucleophile. The same major *cis* product was also obtained with ketone ***ent*-2** (see Scheme S1 in Supporting Information). However, the conclusive proof of the stereochemistry had to await comparison with natural substances[6c] or with reported data for synthetic samples.[9d] There are no stereochemical tasks here, since the *cis* heteroatoms in the methylene lactone **3a** lead to rugulovasine A, while the *trans* heteroatoms in **3b** lead to rugulovasine B. Of note, the low basicity and high nucleophilicity features of the allylic zinc reagent were needed to perform the Dreiding-Schmidt reaction in the presence of two relatively acidic NH



Scheme 1. Retrosynthetic analysis of all four rugulovasine stereoisomers.

Research Article
doi.org/10.1002/ejoc.202200315



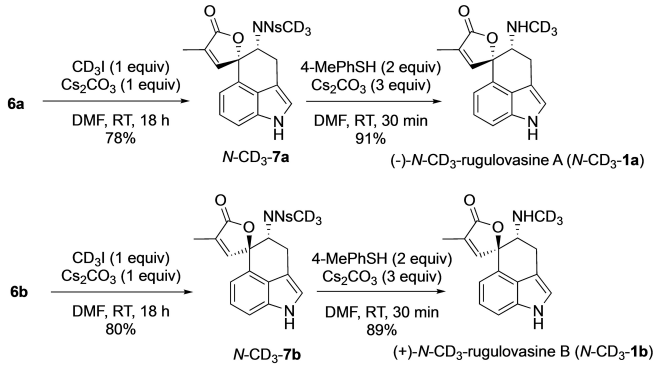
Scheme 2. Synthesis of (−)-rugulovasine A and (+)-rugulovasine B.

groups. Having installed the methylene oxaspirolactone, the next step was to isomerize the *exo*-methylene double bond into the thermodynamically more stable internal alkene (**4a**,**b**), without loss of the optically purity. We found that a catalytic amount of $Ru_3(CO)_{12}$ was able to carry out this transformation.[9e] Similarly, the syntheses of ***ent*-4a**,**b** were accomplished from ***ent*-3a**,**b** (see Scheme S1 in Supporting Information). To complete the asymmetric total synthesis, we needed to find an appropriate direct or indirect methylation approach, which proved challenging. First, we explored the conditions recently reported by Rueping and coworkers for the selective magnesium-catalyzed hydroboration of secondary carbamates, including *N*-Boc-protected amines, to obtain *N*-methyl (and *N*-trideuteromethyl) amines.[15] With substrate **4a** and 3.5 equivalents of HBpin in the presence of 10 mol% $MgBu_2$ under neat reaction conditions, only a trace amount of product was observed. The major product was due to the selective and possible C–N bond cleavage, i.e., deprotection of the *N*-Boc group. The same results also were observed using BH_3 in the presence or in the absence of the Lewis acid $B(C_6F_5)_3$ in THF at room temperature or reflux.[16] Another classical route to secondary *N*-methylamine employs methylation of the carbamate-protected amino group with methyl iodide and NaH in THF or DMF and selective deprotection, since the overall yields of the final products are, in general, higher than those reported by other methods (for example through the *N*-formyl derivative).[16,17] However, when we used these conditions or slight variations, for example with Ag_2O/CH_3I in DMF, the indole nitrogen of **4a** underwent methylation as well. Having realized that the selective *N*-methylation of **4a** was difficult to achieve,[18] we turned our attention to the development of an efficient alternative strategy for the synthesis of either enantiomer of diastereomeric rugulovasine A and B. Thus, we investigated other amine protection/activation groups that are reactive toward site-selective *N*-methylation and *N*-trideuteromethylation while still using mild and reliable formation and cleavage conditions. The 2-nitrobenzenesulfonamide (Ns) is known to generate a nucleophilic anion that can undergo smooth alkylation by conventional methods to give *N*-alkylated sulfonamides, which are selectively deprotected (via Meisenheimer complexes) upon treatment with thiolates under mild reaction conditions, giving secondary amines in near quantitative yields, i.e., Fukuyama amine synthesis.[19] These reports led us to test the reactivity and selectivity of the Ns group in the site-selective mono-*N*-methylation of primary amine **5a**, which was obtained quantitatively by simple treatment of **4a** with HCl in dioxane. The preparation of sulfonamide **6a** was achieved in a 86% total yield by reacting **5a** with NsCl in DCM. Methylation of **6a** proceeded efficiently and selectively upon treatment with methyl iodide in DMF. Following purification of **7a** by flash chromatography, cleavage of the Ns group was achieved by treatment with 4-methylthiophenol in DMF and cesium carbonate. No rearrangement to the more stable six-membered lactam was induced thanks to the mild basic conditions employed in a very short time (30 min).[20] The total synthesis of **1b** was successfully completed by following the established route described above. In terms of the overall efficiency from **2**, compounds **1a** and **1b** were obtained in overall yields of 35% and 16%, respectively. In addition, starting from ***ent*-2**, compounds ***ent*-1a** and ***ent*-1b** were obtained in overall yields of 30% and 14%, respectively (See Scheme S1 in Supporting Information for details).

Importantly, all ^1H and ^{13}C NMR data of both rugulovasines A and B were in excellent agreement with those reported by Martin and co-workers.[9d] High-resolution mass spectrometry of these analytes yielded an *m/z* of 269.1289, indicating a molecular formula of $C_{16}H_{16}N_2O_2$ (calculated *m/z* of 269.1285). The compounds fragmented in a manner typical of the stereoisomeric ergot alkaloids rugulovasines A and B (See Figures S1–S4 in Supporting Information).[21] The optical rotations were also consistent with the reported values for synthetic (−)-rugulovasine A (**1a**) (observed $[\alpha]_D^{20} = -128$ (c = 0.30, MeOH); Lit. $[\alpha]_D^{20} = -142$ (c = 1, MeOH)) and for (+)-rugulovasine A (***ent*-1a**) (observed $[\alpha]_D^{20} = +153$ (c = 0.12, MeOH); Lit. $[\alpha]_D^{20} = +142$ (c = 1, MeOH).[9a]

In light of the recent potential of CD_3-containing molecules as pharmaceuticals as well as their use in analytical profiling and mechanistic studies,[22] we sought to prepare *N*-trideuteromethylated derivatives using our highly versatile route (Scheme 3). Thus, by applying commercially available CD_3I as the methylating agent and the same Fukuyama alkylation procedure above, *N*-CD_3-substituted rugulovasines A and B (*N*-CD_3–**1a**,**b**) could be isolated, after Ns deprotection, in good yield (32% and 16% overall yield, respectively) and with quantitative D-incorporation (see HRMS spectra, Figures S5–S6 in Supporting Information).

Research Article
doi.org/10.1002/ejoc.202200315



Scheme 3. Synthesis of *N*-trideuteromethylated rugulovasines A and B.

The literature on the biological profiles of natural rugulovasines A and B pales in comparison to that of the natural lysergic acid amide class ergot alkaloids or substituted tryptamines. Intriguingly, a recent analysis has indicated that ~84% of approved drugs for CNS diseases are natural products or natural product-inspired molecules, including drugs for Alzheimer's disease.[23] In addition, it is well known that lysergic acid derivatives show distinct and remarkable stereospecificity to brain membrane receptors, wherein D-lysergic acid diethylamide (D-LSD) is more potent than L-LSD, which possesses only 0.1% of the activity of the first.[24] Having expanded the asymmetric synthetic access to all rugulovasine stereoisomers, we were therefore interested in determining the receptor profiles of these compounds and comparing them to reported data for D-LSD.[25] For an initial survey, we selected seven pertinent CNS receptors (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, alpha 2, D_1, D_{2L}, and D_3) and profiled all optically pure stereoisomers at 10 μM and 1 μM (Table 1, entries 1–7). As a group, the rugulovasines were more selective than D-LSD in this receptor panel.

None of the rugulovasine stereoisomers showed significant activity on the dopamine D_1, D_{2L}, and D_3 monoamine receptor family (Table 1, entries 5–7). In addition, they did not have a meaningful effect on the α2 adrenergic receptor (Table 1, entry 4), despite natural racemic rugulovasines A and B having been reported to have centrally mediated hypotensive activity in anesthetized cats.[8] Analogous to D-LSD, all rugulovasine stereoisomers maintained a strong affinity to the serotonin receptors, particularly for the serotonin 1 A (5-HT_{1A}) receptor (Table 1, entry 1). In general, low diastereospecificity differences between rugulovasines A and B were revealed in this receptor panel, whereas a distinct enantiospecificity was observed between (+)- and (−)-rugulovasine B on the serotonin receptors. (+)-Rugulovasine B had very potent binding properties at both 10 μM and 1 μM, whereas (−)-rugulovasine B was less potent at 1 μM and was particularly notable for 5-HT_{2C} (Table 1, entry 3). Possibly, the results for the 5-HT_{2C} receptor versus the 5-HT_{1A} receptor correlate with the mental effects of psychedelics in humans.[26] For those compounds showing a percentage of inhibition >75% at 1 μM, we next assessed their dose-dependent activity on the serotonin receptors.

The purpose of our second-generation functional assays was to determine the effective half-maximal inhibitory concentrations (IC_{50}) for all stereoisomers of rugulovasine on the human 5-HT_{1A} receptor, which is the most widespread of all of the 5-HT receptors and is implicated in the pathogenesis and treatment of anxiety and depressive disorders.[27] As suggested by the preliminary assays, (+)-rugulovasine B was considerably more potent at the 5-HT_{1A} receptor than (−)-rugulovasine B and either enantiomer of rugulovasine A, with an $IC_{50} < 2$ nM (similar to D-LSD) (Table 2).

Given the significant enantiospecificity as well as the high potency of (+)-rugulovasine B on the human 5-HT_{1A} receptor, we explored its activity against other subtypes of serotonin

Table 1. Effects of Rugulovasines and D-LSD Expressed as Percent Inhibition (% Inh.) of Specific Binding of a Radioligand Standard to Selected CNS Receptors.[a]

Entry	Receptor	(−)-Rugulovasine A		(+)-Rugulovasine A		(+)-Rugulovasine B		(−)-Rugulovasine B		D-LSD[b]
		[10 μM]	[1 μM]	[10 μM]	[1 μM]	[10 μM]	[1 μM]	[10 μM]	[1 μM]	[10 μM]
1	Serotonin 5-HT_{1A}	98	92	100	96	100	98	99	74	100
2	Serotonin 5-HT_{2A}	90	50	94	57	99	92	82	40	93
3	Serotonin 5-HT_{2C}	77	22	75	19	95	78	56	9	100
4	α2	35	7	35	0	65	36	7	12	89[c]
5	Dopamine D_1	0	<0	16	<0	52	9	11	2	93
6	Dopamine D_{2L}	37	16	4	22	77	34	22	9	85
7	Dopamine D_3	14	<0	5	<0	56	2	2	<0	78

[a] Biochemical assays were performed using human receptors at Eurofins Cerep France, and the results are presented as a % inhibition of the binding of a radioactively labeled ligand specific for each target. [b] Data from ref. 25. [c] Average of three values: alpha$_{2A}$ (101%), alpha$_{2B}$ (80%), and alpha$_{2C}$ (86%).

Table 2. Effects of Rugulovasines and D-LSD on the Serotonin 1 A Receptor (5-HT_{1A}).[a,b]

Entry	Receptor	(−)-Rugulovasine A [nM]	(+)-Rugulovasine A [nM]	(+)-Rugulovasine B [nM]	(−)-Rugulovasine B [nM]	D-LSD[c] [nM]
1	Serotonin 5-HT_{1A}	37	47	<2	116	3

[a] Biochemical assays were performed using human receptors at Eurofins Cerep France, and the results are based on a 5-point concentration-response curve. [b] Activation potency IC_{50} values are shown, unless otherwise specified. [c] Inhibition constant, Ki; data from ref. [24c].

receptors; to determine the selectivity, the reported activities of D-LSD on the serotonin receptors are also listed (Table 3).

(+)-Rugulovasine B showed a low affinity to 5-HT_{5A} (Table 3, entry 5), whereas it had a moderate potency against 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, and 5-HT_7 (Table 3, entries 2–4 and 7). On the contrary, (+)-rugulovasine B had a good binding affinity to 5-HT_6 (IC_{50} = 10 nM), which is one of the most recently cloned serotonin receptors that, similar to 5-HT_{1A}, plays an important role in depression as well as learning and memory disorders.[28] In particular, (+)-rugulovasine B was highly to moderately selective for 5-HT_{1A} over the other serotonin receptor subtypes tested, except for the 5-HT_6 receptor (< 10-fold). Overall, the 5-HT profile of (+)-rugulovasine B was substantially different from that of D-LSD (Table 3, entries 2–5); thus, we believe that this compound class warrants future investigations due to its selectivity and therapeutic potential.

Conclusion

In summary, we have accomplished the divergent, asymmetric total synthesis of all stereoisomers of rugulovasine utilizing a combination of enantiopure 4-substituted tryptophan derivatives and methacrylate to provide the necessary skeletal features of rugulovasines A and B, with the stereochemical details emerging from the selectivities of the reactions involved. These syntheses proceeded in excellent yields and in a maximum of six steps from known compound **2**, requiring the Dreiding-Schmidt reaction/isomerization to ensure the unsaturated oxaspirolactone moiety of these target molecules and a Fukuyama alkylation procedure to afford the *N*-methyl and *N*-trideuteromethyl secondary amines. Preliminary biological evaluation demonstrated their selectivity for serotonin receptors over dopamine and adrenergic receptors (compared to LSD), excellent affinity for the 5-HT_{1A} receptor, and stereospecificity, with (+)-rugulovasine B being the most interesting isomer in terms of its effective concentration and serotonin receptor selectivity. This strategy shows an increased efficiency with which these rearranged clavines can be synthesized compared to previous methods, opening the door to further exploration of this scaffold. Importantly, this approach may be more amenable to analogue generation relative to prior methods.

Table 3. Effects of (+)-Rugulovasine B and D-LSD on 5-HT Receptors.[a,b]

Entry	Receptor	(+)-Rugulovasine B [nM]	D-LSD[c] [nM]
1	Serotonin 5-HT_{1A}	< 2	3[d]
2	Serotonin 5-HT_{2A}	46	261
3	Serotonin 5-HT_{2B}	58	12000
4	Serotonin 5-HT_{2C}	339	15[d]
5	Serotonin 5-HT_{5A}	13700	9[d,e]
6	Serotonin 5-HT_6	10	6.9[d,e]
7	Serotonin 5-HT_7	34	6.6[d,e]

[a] Biochemical assays were performed using human receptors at Eurofins Cerep France, and the results are based on a 5-point concentration-response curve. [b] IC_{50} values against activation are shown, unless otherwise specified. [c] Data from ref. [24c], unless otherwise specified. [d] Inhibition constant, K_i. [e] Data from ref. [24d].

Acknowledgements

This work was supported by the Italian Ministry for University and Research (MUR, PRIN 2020, 2020AEX4TA project) and University of Urbino grants (DISB_PIERSANTI_PROG_SIC_ALIMENTARE). We thank Prof. Gilberto Spadoni and Prof.ssa Annalida Bedini for helpful discussion for biological activity. We also thank Prof. Michele Menotta for assistance with HRMS analysis. Open Access Funding provided by Universita degli Studi di Urbino Carlo Bo within the CRUI-CARE Agreement.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Asymmetric synthesis · Chirality• Clavine alkaloids · Deuterated compounds · Serotonin receptors

[1] a) S. R. McCabe, P. Wipf, *Org. Biomol. Chem.* **2016**, *14*, 5894–5913; b) D. Jakubczyk, J. Z. Cheng, S. E. O'Connor, *Nat. Prod. Rep.* **2014**, *31*, 1328–1338; c) C. Wallwey, S.-M. Li, *Nat. Prod. Rep.* **2011**, *28*, 496–510; d) N. Gerhards, L. Neubauer, P. Tudzynski, S.-M. Li, *Toxin Rev.* **2014**, *6*, 3281–3295.

[2] a) J. J. Chen, M. Y. Han, T. Gong, J. L. Yang, P. Zhu, *RSC Adv.* **2017**, *7*, 27384–27396; b) L. Haichao, J. Yanxing, *Nat. Prod. Rep.* **2017**, *34*, 411–432; For a nice example: c) S. R. McCabe, P. Wipf, *Synthesis* **2019**, *51*, 213–224.

[3] a) N. R. Tasker, P. Wipf, in *The Alkaloids: Chemistry and Biology*, Vol. 85 (Eds: H.-J. Knölker), Academic Press **2021**, Ch 1; b) P. L. Schiff, *Am. J. Pharm. Educ.* **2006**, *70*, 98.

[4] For a review, see: a) M. Ito, Y. K. Tahara, T. Shibata, *Chem. Eur. J.* **2016**, *22*, 5468–5477; For Biosynthesis, see: b) K.-L. Chen, C.-Y. Lai, M.-T. Pham, R.-J. Chein, Y. Tang, H.-C. Lin, *Org. Lett.* **2020**, *22*, 3302–3306.

[5] a) W. Wang, Y. Mi, X.-P. Cao, Z.-F. Shi, *Org. Lett.* **2019**, *21*, 6603–6607; b) M. Incze, G. Dörnyei, I. Moldvai, E. Temesvári-Major, O. Egyed, C. Szántay, *Tetrahedron* **2008**, *64*, 2924–2929; c) F. R. Petronijevic, P. Wipf, *J. Am. Chem. Soc.* **2011**, *133*, 7704–7707; d) N. D. Jabre, T. Watanabe, M. Brewer, *Tetrahedron Lett.* **2014**, *55*, 197–199; e) W. Wang, J.-T. Lu, H.-L. Zhang, Z.-F. Shi, J. Wen, X.-P. Cao, *J. Org. Chem.* **2014**, *79*, 122–127; f) N. Netz, T. Opatz, *J. Org. Chem.* **2016**, *81*, 1723–1730; g) J.-Q. Chen, L.-L. Song, F.-X. Li, Z.-F. Shi, X.-P. Cao, *Chem. Commun.* **2017**, *53*, 1290212905; h) S. R. McCabe, P. Wipf, *Angew. Chem. Int. Ed.* **2017**, *56*, 324–327; *Angew. Chem.* **2017**, *129*, 330–333; i) S. Chaudhuri, S. Ghosh, S. Bhunia, A. Bisai, *Chem. Commun.* **2018**, *54*, 940–943; j) L. Deng, M. Chen, G. Dong, *J. Am. Chem. Soc.* **2018**, *140*, 9652–9658.

[6] a) M. Abe, S. Ohmomo, T. Ōhashi, T. Tabuchi, *Agric. Biol. Chem.* **1969**, *33*, 469–471; b) S. Yamatodani, Y. Asahi, A. Matsukura, S. Ohmomo, M. Abe, *Agric. Biol. Chem.* **1970**, *34*, 485–487; c) R. J. Cole, J. W. Kirksey, J. Clardy, N. Eickman, S. M. Weinreb, P. Singh, D. Kim, *Tetrahedron Lett.* **1976**, *17*, 3849–3852; d) R. J. Cole, J. W. Kirksey, H. G. Cutler, D. M. Wilson, G. Morgan-Jones, *Can. J. Microbiol.* **1976**, *22*, 741–744; e) J. W. Dorner, R. J. Cole, R. Hill, D. Wicklow, R. H. Cox, *Appl. Environ. Microbiol.* **1980**, *40*, 685–687; f) V. P. Zhelifonova, T. V. Antipova, S. M. Ozerskaya, N. E. Ivanushkina, A. G. Kozlovskii, *Microbiology* **2006**, *75*, 644–648.

[7] They were isolated along with chanoclavine-I and could conceivably originate from an oxidative cyclization of chanoclavine-I. S. J. Fabian, M. D. Maust, D. G. Panaccione, *Appl. Environ. Microbiol.* **2018**, *84*, e01583–e01518.

[8] While the health effects of the rugulovasines are largely understudied, the available data indicate that they induce negative health consequences, see: G. Meurant, in: *Handbook of toxic fungal metabolites*, (Eds: R. J. Cole, R. H. Cox), Academic Press, New York, **1981**, p 528–544. NY and reference 6e.
[9] a) J. Rebek, Y. K. Shue, *J. Am. Chem. Soc.* **1980**, *102*, 5427–5429; b) J. Rebek, Y.-K. Shue, D. F. Tai, *J. Org. Chem.* **1984**, *49*, 3540–3545; c) S. F. Martin, S. Liras, *J. Am. Chem. Soc.* **1993**, *115*, 10450–10451; d) S. Liras, C. L. Lynch, A. M. Fryer, B. T. Vu, S. F. Martin, *J. Am. Chem. Soc.* **2001**, *123*, 5918–5924; e) Y.-A. Zhang, Q. Liu, C. Wang, Y. Jia, *Org. Lett.* **2013**,*15*, 3662–3665.
[10] Divergent total synthesis requires that an identical intermediate be converted, separately, to at least two members of the class of compounds. Divergent total syntheses are distinct from partial total synthesis in which one member is interconverted to a second member of the class of compounds. For a seminal definition, see: C. E. Brotherton, D. L. Boger, *J. Org. Chem.* **1984**, *49*, 4050–4055.
[11] a) F. Bartoccini, A. Regni, M. Retini, G. Piersanti, *Org. Biomol. Chem.* **2021**, *19*, 2932–2940; b) F. Bartoccini, F. Fanini, M. Retini, G. Piersanti, *Tetrahedron Lett.* **2020**, *61*, 151923; c) M. Retini, S. Bartolucci, F. Bartoccini, M. Mari, G. Piersanti, *J. Org. Chem.* **2019**, *84*, 12221–12227; d) F. Bartoccini, S. Bartolucci, M. Mari, G. Piersanti, *Org. Biomol. Chem.* **2016**, *14*, 10095–10100; For our recent examples, see: e) F. Bartoccini, S. Venturi, M. Retini, M. Mari, G. Piersanti, *J. Org. Chem.* **2019**, *84*, 8027–8034; f) F. Bartoccini, M. Casoli, M. Mari, G. Piersanti, *J. Org. Chem.* **2014**, *79*, 3255–3259; g) S. Lucarini, F. Bartoccini, F. Battistoni, G. Diamantini, G. Piersanti, M. Righi, G. Spadoni, *Org. Lett.* **2010**, *12*, 3844–3847.
[12] a) J. Atzrodt, V. Derdau, W. J. Kerr, M. Reid, *Angew. Chem. Int. Ed.* **2018**, *57*, 1758–1784; *Angew. Chem.* **2018**, *130*, 1774–1802; b) T. Pirali, M. Serafini, S. Cargnin, A. A. Genazzani, *J. Med. Chem.* **2019**, *62*, 5276–5297.
[13] a) E. Öhler, K. Reininger, U. Schmidt, *Angew. Chem. Int. Ed.* **1970**, *9*, 457–458; *Angew. Chem.* **1970**, *82*, 480–481; b) A. Löffler, R. J. Pratt, H. P. Rüesch, A. S. Dreiding, *Helv. Chim. Acta* **1970**, *53*, 383–403.
[14] For review on Uhle's Ketone, see: F. Bartoccini, G. Piersanti, *Synthesis* **2021**, *53*, 1396–1408.
[15] M. Magre, M. Szewczyk, M. Rueping, *Org. Lett.* **2020**, *22*, 3209–3214.
[16] Reduction with LAH or $LiAlH(OMe)_3$ of **4a**,**b** gave only a complex mixture of products, probably with the concomitant reduction of lactone and/or double bonds. The reduction of formamide derivatives also has been used as a means of *N*-methylation. a) K. S. Chu, G. R. Negrete, J. P. Konopelski, *J. Org. Chem.* **1991**, *56*, 5196–5201. Therefore, **4a**,**b** was treated with acetic anhydride and formic acid to provide the *N*-formyl derivatives **S1a** and **S1b** in 66% and 58% yield, respectively. b) R. R. Knapp, V. Tona, T. Okada, R. Sarpong, N. K. Garg, *Org. Lett.* **2020**, *22*, 8430–8435. This product was then chemoselectively reduced by reaction with 1 M borane in THF to afford **1a** and **1b** in 47% and 39% yield, respectively. Although the product could be obtained by this route, the modest yields of the formylation and reduction step as well as its problematic purification due to amine-borane complexation led us to explore alternative routes to the final product (See Supporting Information for details).
[17] For a review, see: a) Y. Chen, in: *The Chemical Transformations of C1 Compounds Vol. 2* (Eds: K. Ding, X.-F. Wu, B. Han, Z. Liu), Wiley-VCH, GmbH, **2022**, pp 1475–1576; b) L. Aurelio, R. T. C. Brownlee, A. B. Hughes, *Chem. Rev.* **2004**, *104*, 5823–5846.
[18] Protection of the indole NH prior to the *N*-methylation step would have been a solution: a) P. A. Grieco, Y. S. Hon, A. Perez-Medrano, *J. Am. Chem. Soc.* **1988**, *110*, 1630–1631; b) Y. Hirai, K. Yokota, T. Momose, *Heterocycles* **1994**, *39*, 603–612; c) P. Ashworth, B. Broadbelt, P. Jankowski, P. Kocienski, A. Pimm, R. Bell, *Synthesis* **1995**, 199–206 and reference 9e.
[19] a) T. Fukuyama, C. K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373–6374:; b) L. Yang, K. Chiu, *Tetrahedron Lett.* **1997**, *38*, 7307–7310; c) S. Sikandar, A. F. Zahoor, S. Naheed, B. Parveen, K. G. Ali, R. Akhtar, *Mol. Diversity* **2021**, *26*, 589–628.
[20] For a nice example of protection/methylation/deprotection with nosyl groups on free tryptamines on solid phase, see: F. Cardullo, D. Donati, V. Fusillo, G. Merlo, A. Paio, M. Salaris, A. Solinas, M. Taddei, *J. Comb. Chem.* **2006**, *8*, 834–840.
[21] L. de Medeiros, J. da Silva, L. Abreu, L. Pfenning, C. Silva, S. Thomasi, T. Venâncio, K.-H. van Pée, K. Nielsen, E. Rodrigues-Filho, *Molecules* **2015**, *20*, 17627–17644.
[22] a) Q. Sun, J.-F. Soulé, *Chem. Soc. Rev.* **2021**, *50*, 10806–10835; b) J. Steverlynck, R. Sitdikov, M. Rueping, *Chem. Eur. J.* **2021**, *27*, 11751–11772.
[23] S. S. Bharate, S. Mignani, R. A. Vishwakarma, *J. Med. Chem.* **2018**, *61*, 10345–10374.
[24] LSD, like rugulovasines, contains two stereogenic centers, so again four stereoisomers exist: two diastereoisomers, each existing as a pair of enantiomers: therefore, four optically-active LSD isomers are possible and known. These are *d*- and *l*-LSD and *d*- and *l*-isolysergic acid diethylamide. Only the *d*-LSD isomer has psychoactive properties. In this manuscript D-LSD [CAS Registry Number 50–37-3] correspond to *d*-LSD or LSD in agreement with a) J. P. Bennett, S. H. Snyder, *Brain Res.* **1975**, *94*, 523–544; b) R. G. dos Santos, J. C. Bouso, M. A. Alcazar-Corcoles, J. E. C. Hallak, *Expert Rev. Clin. Pharmacol.* **2018**, *11*, 889–902; c) A. Rickli, O. D. Moning, M. C. Hoener, M. E. Liechti, *Eur. Neuropsychopharmacol.* **2016**, *26*, 1327–1337; d) D. E. Nichols, S. Frescas, D. Marona-Lewicka, D. M. Kurrasch-Orbaugh, *J. Med. Chem.* **2002**, *45*, 4344–4349.
[25] B. L. Roth, K. Baner, R. Westkaemper, D. Siebert, K. C. Rice, S. Steinberg, P. Ernsberger, R. B. Rothman, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 11934–11939.
[26] A strong correlation was described between psychoactive doses of hallucinogens and their respective potency at the $5\text{-}HT_2$ receptor. Most data indicate a specific $5\text{-}HT_{2A}$ mechanism, although a $5\text{-}HT_{2C}$ effect cannot be ruled out. For selected references, see: a) R. A. Glennon, M. McKenney, J. D. Titeler, *Life Sci.* **1984**, *35*, 2505–2511; b) M. Titeler, R. A. Lyon, R. A. Glennon, *Psychopharmacology* **1988**, *94*, 213–216; c) B. L. Roth, D. L. Willins, K. Kristiansen, W. K. Kroeze, *Pharmacol. Ther.* **1998**, *79*, 231–257; d) S. Mantegani, E. Brambilla, M. Varasi, *Il Farmaco* **1999**, *54*, 288–296; e) D. E. Nichols, *Pharmacol. Ther.* **2004**, *101*, 131–181.
[27] a) D. E. Nichols, C. D. Nichols, *Chem. Rev.* **2008**, *108*, 1614–1641; b) E. Lacivita, M. Leopoldo, F. Berardi, R. Perrone, *Curr. Top. Med. Chem.* **2008**, *8*, 1024–1034.
[28] a) L. E. Schechter, Q. Lin, D. L. Smith, G. Zhang, Q. Shan, B. Platt, M. R. Brandt, L. A. Dawson, D. Cole, R. Bernotas, A. Robichaud, S. Rosenzweig-Lipson, C. E. Beyer, *Neuropsychopharmacology* **2008**, *33*, 1323–1335; b) M. V. King, C. A. Marsden, K. C. F. Fone, *Trends Pharmacol. Sci.* **2008**, *29*, 482–492.

Manuscript received: March 16, 2022
Revised manuscript received: April 7, 2022
Accepted manuscript online: April 8, 2022