Synthesis of Azepino[4,5-*b*]indolones by an Intramolecular Cyclization of Unsaturated Tryptamides

John Eugene Nidhiry, Kavirayani R. Prasad*

Department of Organic Chemistry, Indian Institute of Science, Sir C. V. Raman Avenue, Bangalore 560012, India
Fax +91(80)23600529; E-mail: prasad@orgchem.iisc.ernet.in

Received: 03.07.2014; Accepted after revision: 15.08.2014

Dedicated to Prof. H. Ila, an outstanding organic chemist from India, on the occasion of her 70th birthday

Abstract: A facile general route for the synthesis of azepino[4,5-*b*]indolones is presented. The strategy involves a Brønsted acid assisted intramolecular cyclization of unsaturated tryptamides. The methodology developed has been applied to the synthesis of the ABCD tetracyclic core of the natural product tronocarpine.

Key words: alkaloids, azepino[4,5-*b*]indolone, tronocarpine, tryptamide, ethyl lactate

The presence of structurally diverse molecular architectures is a characteristic feature in naturally occurring indole alkaloids.[1] The development of novel synthetic methodologies to access such frameworks is of immense importance in heterocyclic chemistry.[2] The azepino[4,5-*b*]indolone unit **1a** is a structural motif found in indole alkaloids such as tronocarpine (**2**),[3] malassezindole A (**3a**) and malassezindole B (**3b**)[4] and lasiodipline F (**4**)[5] (Figure 1). The presence of a quaternary stereogenic center adjacent to the C-2 position of the indole ring is a common feature in these natural products. While dopamine[6] and opioid[7] receptor binding abilities have been attributed to synthetic derivatives containing an azepino[4,5-*b*]indolone unit, the potential of such compounds to treat Alzheimer's disease has also been reported.[8]

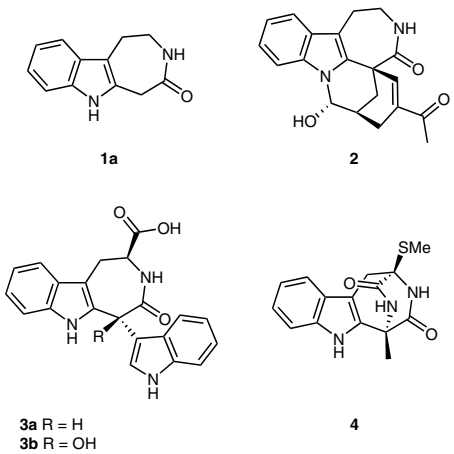


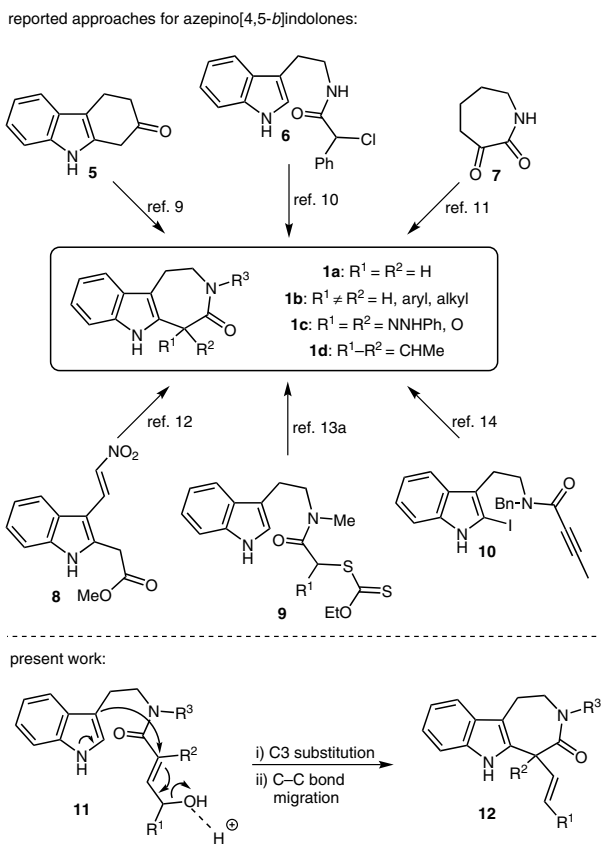
Figure 1 The azepino[4,5-*b*]indolone framework **1a** and related natural products **2**–**4**

The first synthesis of an azepino[4,5-*b*]indolone, such as **1a**, was reported by Teuber et al. starting from dihydrocarbazolone **5** using a Schmidt reaction.[9] Later, structurally similar compounds such as **1b** and **1c** were synthesized by Freter[10] via an acid-mediated electrophilic cyclization of phenylchloroacetyltryptamide **6** and by Glushkov et al.[11] using a Fischer indole synthesis with α-oxocaprolactam **7**. Hydrogenation–lactamization of the nitro-olefin **8** derived from indolyl-2-acetate via a nitro-Mannich reaction were the key steps in the synthesis of **1a**, described by Mahboobi and Bernauer.[12] A xanthate-mediated intramolecular annulation of tryptamide **9** using lauroyl peroxide was reported by Zard's group for the synthesis of **1b**,[13a] while an analogous intermolecular version of this reaction was used by Martinez's group for the synthesis of such structures.[13b] Van der Eycken and co-workers have reported a Pd-catalyzed intramolecular acetylene hydroarylation reaction of 2-iodotryptamide derivative **10** for the synthesis of **1d** (Scheme 1).[14]

Although simple azepino[4,5-*b*]indolones can be accessed by the aforementioned methods, approaches to the synthesis of compounds such as **1b**, possessing a quaternary stereogenic center, are limited.[13b] The pharmacological importance of the azepino[4,5-*b*]indolone framework coupled with our interest in indole alkaloids,[15] led us to devise an approach involving an intramolecular cyclization of α,β-unsaturated tryptamide **11** to access compounds such as **12** (Scheme 1). Herein, we disclose a simple and general route to synthesize azepino[4,5-*b*]indolones possessing a quaternary stereogenic center via Brønsted acid mediated intramolecular S_N' reaction.

As outlined in Scheme 2, synthesis of the requisite precursors **11a** and **11b** was accomplished from (*S*)-ethyl lactate. DIBAL-H reduction of α-silyloxy ester **13a** to the corresponding aldehyde and further Wittig–Horner olefination with phosphorane **14** furnished the α,β-unsaturated ester **15a** in 73% yield. Hydrolysis of the ester with LiOH afforded the corresponding silyloxy acid **16a** along with the silyl-deprotected acid. To avoid a cumbersome separation, the mixture was converted into the silyloxy silyl ester, which, on reaction with K_2CO_3, afforded the pure silyloxy acid **16a** in 83% yield. Amidation of the silyloxy acid **16a** with the corresponding tryptamine afforded tryptamides **17a** and **17b** in 75% and 79% yields, respectively. Treatment of the tryptamides **17a** and **17b** with

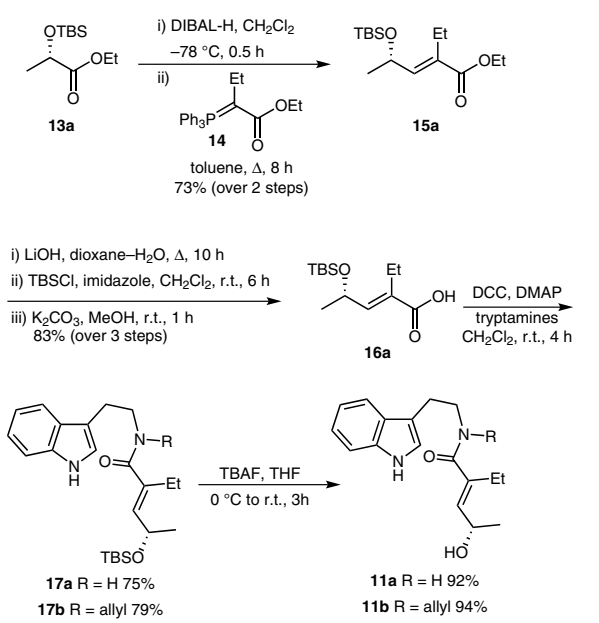
SYNLETT 2014, 25, 2585–2590
Advanced online publication: 02.10.2014
DOI: 10.1055/s-0034-1379083; Art ID: st-2014-d0562-l



Scheme 1 Reported approaches for the synthesis of azepino[4,5-*b*]indolone framework; the current approach presented herein

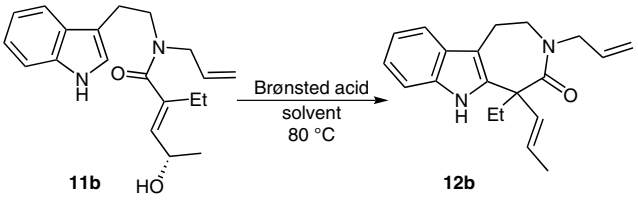
TBAF furnished the hydroxy tryptamides **11a** and **11b** in good yields.

After accessing the required tryptamides **11a** and **11b**, the key intramolecular cyclization was attempted under a series of conditions. Initial reaction of hydroxy tryptamide **11a** with TFA gave a mixture of unidentifiable compounds, possibly due to interference from the free amide NH, whereas reaction of *N*-allyl tryptamide **11b** with TFA did not progress at room temperature. Heating the reaction mixture to 80 °C, furnished the corresponding azepino[4,5-*b*]indolone **12b** possessing a quaternary stereogenic center in 17% yield via an intramolecular S_N'-type cyclization, thus indicating that a secondary amide was necessary in the substrate. Considering **11b** as the model substrate, the optimization of the reaction conditions was carried out by screening different Brønsted acids and solvents. The results of this study are compiled in Table 1. Strong Brønsted acids such as CF_3SO_3H and $MeSO_3H$ did not furnish the desired product, while the use of PTSA gave the desired product **12b** in an improved 55% yield (entries 2–4, Table 1). Employing (+)-camphorsulfonic acid (CSA) afforded **12b** in an increased 71% yield (entry 5, Table 1). The use of more equivalents of (+)-CSA (5 equiv) reduced the reaction time, while a catalytic amount of (+)-CSA (20 mol%) decreased the reaction rate and lowered the yield significantly (entries 6 and 7, Table 1). When the reaction was performed in 1,2-DCE a marginal drop in the yield was observed, while the use of acetonitrile as solvent gave **12b** in only 36% yield (entries 9 and 10, Table 1). Additionally, we were also curious to find out if the chirality transfer from the allylic alcohol was



Scheme 2 Synthetic route for the preparation of tryptamides **11a** and **11b**

Table 1 Optimization of the Reaction Conditions[a]



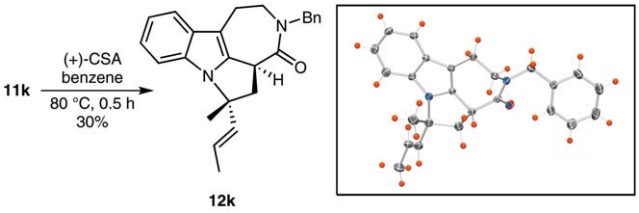
Entry	Reagent	Solvent	Equiv	Time (h)	Yield (%)[b]
1	TFA	benzene	2	0.5	17
2	CF_3SO_3H	benzene	2	0.5	0[c]
3	$MeSO_3H$	benzene	2	0.5	0[c]
4	PTSA	benzene	2	2	55
5	**(+)-CSA**	benzene	**2**	**2**	**71**
6	(+)-CSA	benzene	5	1	65
7	(+)-CSA	benzene	0.2	24	51
8	(–)-CSA	benzene	2	2	63
9	(+)-CSA	DCE	2	2.5	62
10	(+)-CSA	MeCN	2	1.5	36

[a] All reactions were performed at 0.1 M dilution at 80 °C.
[b] Isolated yield after silica gel column chromatography.
[c] The reaction was performed at 0 °C; the starting material showed completion by TLC. TFA = trifluoroacetic acid, PTSA = *p*-toluenesulfonic acid, CSA = camphorsulfonic acid, DCE = 1,2-dichloroethane.

complete in the formation of **12b**, which consequently would provide an insight into the reaction mechanism. Chiral HPLC analysis of **12b** showed an enantiomeric ratio of 60:40 (20% ee) indicating a loss of chirality in the reaction process.[16] An enantiomeric excess of 20% suggests that the reaction predominantly proceeds through an S_N1' pathway via a carbocationic intermediate.[17] The structure of **12b** was unambiguously confirmed by single crystal X-ray diffraction analysis.[18]

To explore the scope and limitations of the reaction, the synthesis of precursors **11c**–**m** (Figure 2)[19] was accomplished using a similar protocol as described in Scheme 2. The synthesized hydroxy tryptamides **11c**–**j** were subjected to the optimized reaction conditions of two equivalents of (+)-CSA in benzene at 80 °C, and the results are summarized in Table 2. It was found that the reaction of tryptamides **11c**–**f** derived from ethyl lactate **13a** comprising a methyl, benzyl and *p*-methoxy benzyl substituent on the nitrogen of tryptamine, afforded the corresponding azepino[4,5-*b*]indolones **12c**–**f** possessing quaternary stereogenic centers in 60–71% yields (entries 1–4, Table 2). Substrate **11g**, possessing no substitution on the double bond in the unsaturated tryptamide furnished the azepino[4,5-*b*]indolone **12g** resulting from migration of the double bond to form the more stable conjugated lactam as separable *E*/*Z* isomers in 2:3 ratio, respectively (entry 5, Table 2).[20] Tryptamide **11h** derived from methyl 3-hydroxyvalerate gave the azepino[4,5-*b*]indolone **12h** in 40% yield (entry 6, Table 2). The reaction of tryptamide **11i** containing a primary allylic alcohol was very sluggish (24 h) and the desired product **12i** was obtained in only 29% yield along with a mixture of unidentifiable compounds (entry 7, Table 2). Substrate **11j** with a protected indole NH also delivered the desired product **12j** in 47% yield (entry 8, Table 2). Therefore, it can be inferred that tryptamides derived from ethyl lactate possessing a secondary amide NH, a secondary allylic hydroxy group and a free indole NH are comparatively better substrates for undergoing an intramolecular S_N'-type cyclization to furnish the corresponding azepino[4,5-*b*]indolones in good yields.

Interestingly, the substrate **11k** having extended conjugation, furnished the tetracyclic compound **12k**, probably resulting from the initial cyclization to form the azepino[4,5-*b*]indolone followed by subsequent capture of the more stable carbocationic intermediate by the indole nitrogen (Scheme 3). The relative configurations of the newly formed stereogenic centers were assigned on the basis of X-ray crystal structure analysis of **12k**.[21]



Scheme 3 Formation of a tetracyclic azepino[4,5-*b*]indolone **12k** and an ORTEP diagram of **12k** at 50% probability

The *N*-allyl tryptamide **11l** derived from methyl mandelate furnished the azepino[4,5-*b*]indolone **12l** in only 23% yield along with a mixture of unidentifiable compounds. While in case of the *N*-benzyl analogue **11m**, it is worth noting that the formation of an azonino[5,4-*b*]indolone **18** takes place in 23% yield along with the desired azepino[4,5-*b*]indolone **12m**. The formation of a stabilized π-allyl carbocation leads to two possible modes of nucleophilic attack of the indole ring, *viz*. an S_N1 pathway resulting in **18** and S_N1' pathway leading to **12m** (Scheme 4). Interestingly, the isomerization of the *E*-olefin to the *Z*-olefin occurred during the course of formation of **18** as established by the X-ray crystallographic analysis.[22]

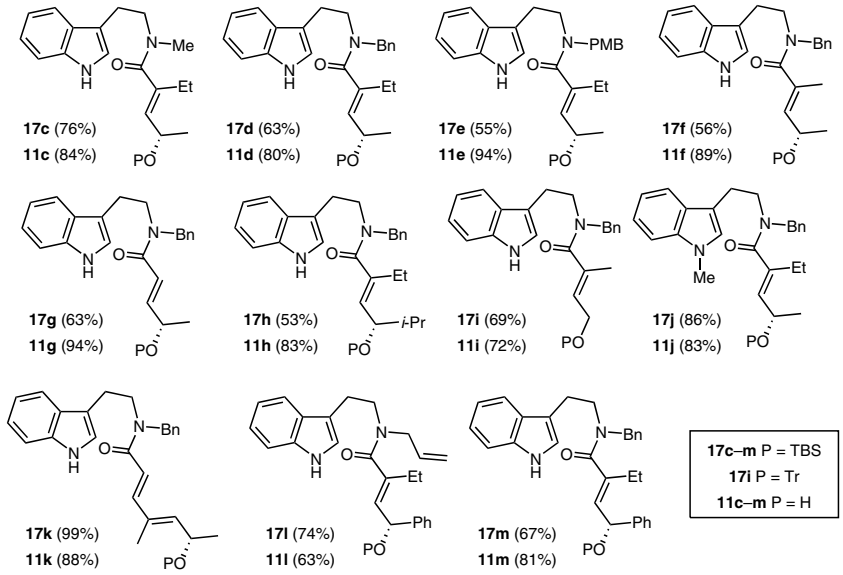
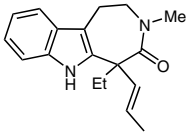
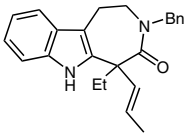
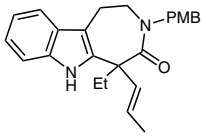
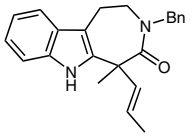
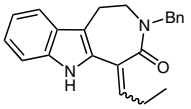
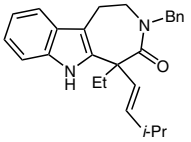
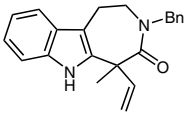
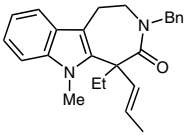


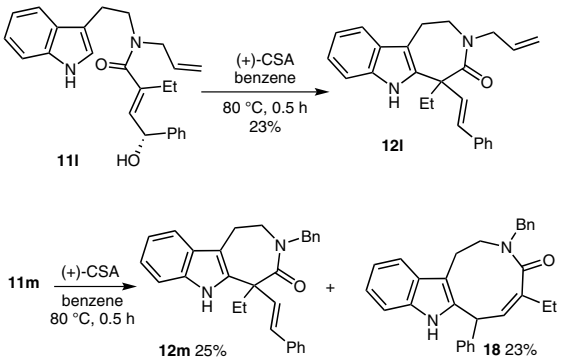
Figure 2 Yields of tryptamides **17c**–**m** and hydroxy tryptamides **11c**–**m**

Table 2 Substrate Scope of the Intramolecular Cyclization[a]

Entry	Substrate	Azepino[4,5-*b*]indolone	Time (h)	Yield (%)[b]
1	**11c**	 **12c**	2.5	71
2	**11d**	 **12d**	1.5	61
3	**11e**	 **12e**	1	60
4	**11f**	 **12f**	2.5	64
5	**11g**	 **12g**	3	56
6	**11h**	 **12h**	3	40
7	**11i**	 **12i**	24	29
8	**11j**	 **12j**	1.5	47

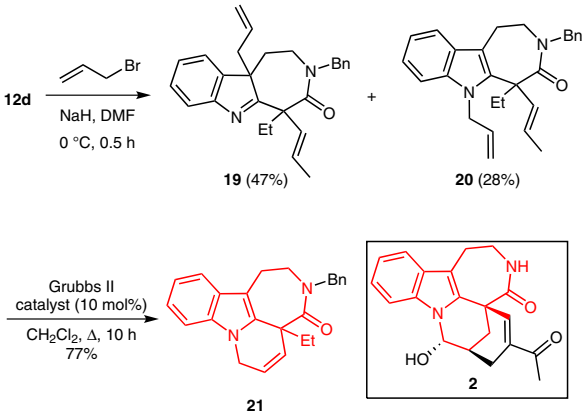
[a] Reaction conditions: substrate (0.1 mmol), (+)-CSA (0.2 mmol) in benzene (1 mL) at 80 °C.
[b] Isolated yield after silica gel column chromatography.

An application of the developed methodology for the synthesis of the ABCD core of the indole alkaloid tronocarpine (**2**)[23] was then considered. Accordingly, allylation of azepino[4,5-*b*]indolone **12d** with allyl bromide afford-



Scheme 4 An unexpected formation of azonino[5,4-*b*]indolone **18**

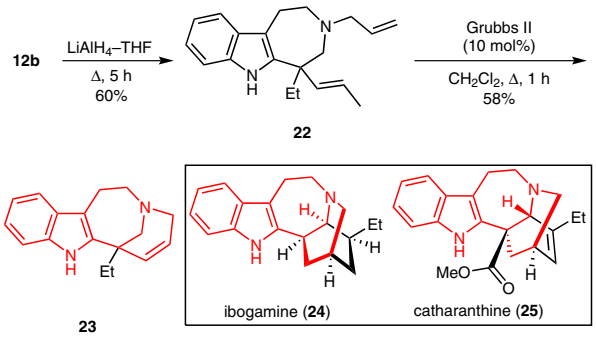
ed a mixture of indolones **19** and **20** resulting from the allylation of **12d** at C3 and the indole NH in 47% and 28% yields, respectively. Subsequent treatment of **20** with Grubbs' 2nd generation catalyst[24] in refluxing CH_2Cl_2 furnished the ABCD tetracyclic core **21** of tronocarpine (**2**) in good yield (Scheme 5).



Scheme 5 Synthesis of ABCD ring system of tronocarpine (**2**)

In another application, **12b** was reduced to the corresponding azepino[4,5-*b*]indole **22** with $LiAlH_4$ in 60% yield. Ring-closing metathesis reaction of **22** with Grubbs' 2nd generation catalyst furnished the tetracycle **23** in 58% yield, which forms the core of a number of indole alkaloids such as ibogamine (**24**) and catharanthine (**25**) (Scheme 6).

In summary, a facile route to azepino[4,5-*b*]indolones possessing a quaternary stereogenic center via Brønsted acid mediated intramolecular cyclization has been developed. A comparative study was conducted to examine the effect of various substituents in determining the outcome of the reaction. Substrates derived from ethyl lactate proved to be the most effective. During the course of this study, an interesting formation of a tetracyclic azepino[4,5-*b*]indolone **12k** and also that of azonino[5,4-*b*]indolone **18** were observed. The presence of alkyl and alkenyl moieties in the quaternary center allowed the functionalization of these compounds and was subsequently employed to access the ABCD tetracyclic core of



Scheme 6 Synthesis of tetracyclic core of ibogamine (**24**) and catharanthine (**25**)

tronocarpine. Currently, efforts are underway to develop an enantioselective version of the intramolecular cyclization and also to synthesize some of the natural products possessing the azepino[4,5-*b*]indolone framework.

Acknowledgment

J.E.N. thanks the Council of Scientific and Industrial Research (CSIR), New Delhi for a Research Fellowship. The authors are very grateful to Mr. K. Durgaprasad and Prof. T. N. Guru Row of the Solid State and Structural Chemistry Unit, Indian Institute of Science for their kind help in the single crystal X-ray diffraction analysis of some of the compounds.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

References and Notes

(1) (a) Veale, C. G. L.; Davies-Coleman, M. T. In *The Alkaloids: Chemistry and Biology*; Vol. 73; Knölker, H.-J., Ed.; Academic Press: Amsterdam, **2014**. (b) Bhat, V.; Dave, A.; MacKay, J. A.; Rawal, V. H. In *The Alkaloids: Chemistry and Biology*; Vol. 73; Knölker, H.-J., Ed.; Academic Press: Amsterdam, **2014**. (c) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. *Nat. Prod. Rep.* **2013**, *30*, 694. (d) Rahman, A. U.; Basha, A. *Indole Alkaloids*; Harwood Academic Publishers: Amsterdam, **1998**.

(2) (a) Bauer, I.; Knölker, H.-J. *Top. Curr. Chem.* **2012**, *309*, 203. (b) Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608. (c) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (d) Agarwal, S.; Cammerer, S.; Filali, S.; Frohner, W.; Knoll, J.; Krahl, M. P.; Reddy, K. R.; Knölker, H.-J. *Curr. Org. Chem.* **2005**, *9*, 1601. (e) Gribble, G. W. *Pure Appl. Chem.* **2003**, *75*, 1417. (f) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (g) Sapi, J.; Massiot, G. In *Monoterpenoid Indole Alkaloids, The Chemistry of Heterocyclic Compounds*; Vol. 25; Saxton, J. E.; Taylor, E. C., Eds.; Wiley: New York, **1994**.

(3) Kam, T.-S.; Sim, K.-M.; Lim, T.-M. *Tetrahedron Lett.* **2000**, *41*, 2733.

(4) Irlinger, B.; Bartsch, A.; Kramer, H.-J.; Mayser, P.; Steglich, W. *Helv. Chim. Acta* **2005**, *88*, 1472.

(5) Wei, W.; Jiang, N.; Mei, Y. N.; Chu, Y. L.; Ge, H. M.; Song, Y. C.; Ng, S. W.; Tan, R. X. *Phytochemistry* **2014**, *100*, 103.

(6) Kraxner, J.; Hubner, H.; Gmeiner, P. *Arch. Pharm. Pharm. Med. Chem.* **2000**, *333*, 287.

(7) Asche, G.; Kunz, H.; Nar, H.; Köppen, H.; Briem, H.; Pook, K.-H.; Schiller, P. W.; Chung, N. N.; Lemieux, C.; Esser, F. *J. Peptide Res.* **1998**, *51*, 323.

(8) Gordillo-Cruz, R. E.; Rentería-Gómez, A.; Islas-Jácome, A.; Cortes-García, C. J.; Díaz-Cervantes, E.; Robles, J.; Gámez-Montaño, R. *Org. Biomol. Chem.* **2013**, *11*, 6470.

(9) Teuber, H.-J.; Cornelius, D.; Wolker, U. *Liebigs Ann. Chem.* **1966**, *696*, 116.

(10) Freter, K. *Liebigs Ann. Chem.* **1969**, *721*, 101.

(11) Glushkov, R. G.; Zasosova, I. M.; Ovcharova, I. M.; Solov'eva, N. P.; Sheinker, Y. N. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1979**, *15*, 780.

(12) Mahboobi, S.; Bernauer, K. *Helv. Chim. Acta* **1988**, *71*, 2034.

(13) (a) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem. Int. Ed.* **2000**, *39*, 731. (b) Reyes-Gutiérrez, P. E.; Torres-Ochoa, R. O.; Martínez, R.; Miranda, L. D. *Org. Biomol. Chem.* **2009**, *7*, 1388.

(14) Peshkov, V. A.; Van Hove, S.; Donets, P. A.; Pereshivko, O. P.; Van Hecke, K.; Van Meervelt, L.; Van der Eycken, E. V. *Eur. J. Org. Chem.* **2011**, 1837.

(15) (a) Prasad, K. R.; Nidhiry, J. E.; Sridharan, M. *Tetrahedron* **2014**, *70*, 4611. (b) Nidhiry, J. E.; Prasad, K. R. *Tetrahedron* **2013**, *69*, 5525. (c) Prasad, K. R.; Nidhiry, J. E. *Synlett* **2012**, *23*, 1477.

(16) **Representative Procedure for the Preparation of Azepino[4,5-*b*]indolones**: To a solution of hydroxy tryptamide **11b** (33 mg, 0.10 mmol) in anhyd benzene (1 mL) under nitrogen atmosphere was added (+)-CSA (46 mg, 0.2 mmol). The resulting mixture was heated to 80 °C and was stirred at that temperature for 2 h. After completion of reaction (as indicated by TLC), the reaction mixture was cooled to r.t. and quenched by the addition of sat. $NaHCO_3$ solution to a pH value of ca. 9 and was then extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried over anhyd Na_2SO_4. The crude residue obtained after filtration and evaporation of the solvent was purified by silica gel column chromatography using petroleum ether–EtOAc (4:1) as eluent to afford azepino[4,5-*b*]indolone **12b** (22 mg, 71%) as a pale yellow solid. Recrystallization of **12b** from petroleum ether–EtOH solvent system (9:1) gave crystals suitable for X-ray diffraction analysis; mp 168–170 °C; $[\alpha]_D^{24}$ –26.3 (*c*, 0.35, $CHCl_3$), corresponding to 20% ee as determined by chiral HPLC analysis [CHIRACEL OD-H, isopropanol–hexane (5:95), flow rate = 1.0 mL/min, t_R (major) = 12.11 min, t_R (minor) = 28.76 min]. IR (KBr): 3387, 2919, 1625, 1464, 1233 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.95 (br s, 1 H), 7.47 (d, *J* = 8.0 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 7.19 (t, *J* = 7.2 Hz, 1 H), 7.11 (t, *J* = 7.2 Hz, 1 H), 5.87 (ddt, *J* = 17.2, 9.2, 5.6 Hz, 1 H), 5.72 (dd, *J* = 15.6, 1.6 Hz, 1 H), 5.27 (dq, *J* = 15.6, 6.4 Hz, 1 H), 5.21 (dd, *J* = 16.0, 1.2 Hz, 1 H), 5.19 (d, *J* = 9.2 Hz, 1 H), 4.28 (dd, *J* = 15.2, 5.6 Hz, 1 H), 4.02–4.15 (m, 2 H), 3.41 (dt, *J* = 15.2, 4.0 Hz, 1 H), 2.88–3.05 (m, 2 H), 2.57 (sext, *J* = 7.2 Hz, 1 H), 1.92 (sext, *J* = 7.2 Hz, 1 H), 1.67 (d, *J* = 6.4 Hz, 3 H), 0.97 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 135.1, 134.8, 133.7, 131.8, 128.3, 125.6, 121.9, 119.2, 117.9, 116.9, 112.6, 110.5, 55.4, 52.0, 45.8, 31.9, 24.7, 17.6, 10.7. HRMS: *m/z* [M + Na] calcd for $C_{20}H_{24}N_2O$: 331.1786; found: 331.1786.

(17) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure*; John Wiley & Sons: New Jersey, **2007**, 6th ed., 469–473.

(18) For an ORTEP diagram of **12b**, see the Supporting Information. The crystal structure data have been deposited with the Cambridge Crystallographic Data Centre (CCDC

No. 1000488). The data can be accessed free of charge from CCDC at: www.ccdc.cam.ac.uk/data_request/cif.

(19) The experimental procedures for the preparation of compounds **11c**–**m** are described in the Supporting Information.

(20) The structure of *E*-isomer was elucidated by single crystal X-ray diffraction analysis. For an ORTEP diagram, see the Supporting Information. The crystal structure data have been deposited with the Cambridge Crystallographic Data Centre (CCDC No. 980704).

(21) The crystal structure data have been deposited with the Cambridge Crystallographic Data Centre (CCDC No. 995842).

(22) For an ORTEP diagram of **18**, see the Supporting Information. The crystal structure data have been deposited with the Cambridge Crystallographic Data Centre (CCDC No. 980703).

(23) For approaches towards the pentacyclic and tetracyclic cores of tronocarpine, see: (a) Torres-Ochoa, R. O.; Reyes-Gutiérrez, P. E.; Martínez, R. *Eur. J. Org. Chem.* **2014**, 48. (b) Magolan, J.; Kerr, M. A. *Org. Lett.* **2006**, *8*, 4561. (c) Also see ref. 13a.

(24) Grubbs, R. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 3760; *Angew*. *Chem*. **2006**, *118*, 3845.

