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Hypoiodite-Catalyzed Chemoselective Tandem Oxidation of Homotryptamines to Peroxy- and Epoxytetrahydropyridoindolenines

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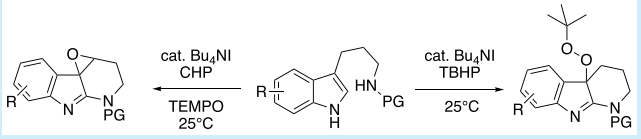
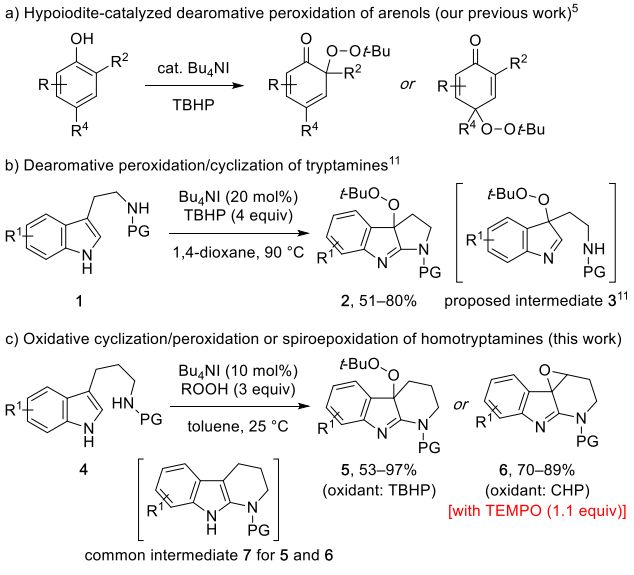
ABSTRACT: We developed the hypoiodite-catalyzed tandem dearomative peroxycyclization of homotryptamine derivatives to peroxytetrahydropyridoindolenines under mild conditions. During the course of a mechanistic study, we found that a tandem oxidative cyclization/epoxidation as an unexpected reaction proceeded in the presence of TEMPO as an additive. Intramolecular oxidative aminocyclization of homotryptamines at the C-2 position would give tetrahydropyridoindole, a common intermediate for both reactions. Control experiments suggested that while oxidative coupling with TBHP at the C-3 position might afford peroxyindolenines, a preferential electrophilic addition of TEMPO$^+$, which might be generated in situ by the hypoiodite-catalyzed oxidation of TEMPO, at C-3 position followed by elimination and epoxidation might give epoxyindolenines. This serendipitous finding prompted us to develop a chemoselective divergent synthesis of peroxy- and epoxyindolenines by simple modification of the reaction conditions.



Indole alkaloids constitute one of the largest groups of nitrogen-containing secondary metabolites, and more than 4000 indole alkaloids have already been found in nature.[1] Because of their significant and wide range of biological activities, the development of efficient methods for the synthesis of indole alkaloids is one of the most important topics in synthetic organic chemistry, especially for drug discovery.[1,2] Beside indole, the most common structural motifs found in various indole-derived alkaloids are indolenine, indoline, and oxindole.[1] Oxidative dearomative functionalization of indoles is one of the most important strategies for construction of these structures.[3] Various methods have been developed for the dearomative functionalization of indoles.[3] However, previous methods often rely on the use of precious transition metal catalysts and/or potentially explosive oxidants.[3]

We have developed the quaternary ammonium hypoiodite-catalyzed[4] oxidative dearomative coupling of arenols.[5,6] In this context, given the important biological activities (i.e., antitumor, antibacterial, etc.) of the peroxy functionality of numerous pharmaceutical compounds,[7] we have reported the dearomative peroxidation of electron-rich arenols with *tert*-butyl hydroperoxide (TBHP) as an oxidant and a coupling partner (Scheme 1a).[5] We envisioned that peroxyindolenines[8] might be accessed from the oxidative dearomative coupling of indoles with alkyl hydroperoxides via a similar umpolung strategy of indoles. During our investigation of the oxidative dearomative coupling of indoles,[9,10] Zhong and colleagues reported the oxidative dearomative peroxycyclization of tryptamines **1** to peroxypyrroloindolenines **2** using a catalytic

Scheme 1. Tandem Oxidative Dearomative Peroxidation and Epoxidation of Indole Derivatives



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amount of *n*-tetrabutylammonium iodide (Bu_4NI) in the presence of TBHP as an oxidant and coupling reagent (Scheme 1b).[11] The reaction required high temperatures to proceed, and the authors proposed an intermolecular radical coupling mechanism to give peroxyindolenine intermediates **3** before the oxidative cyclization to **2**. On the other hand, the authors also investigated the biological activities, which revealed a promising antitumor activity of these adducts, in which, importantly, both the indolenine and the peroxy units were found to be crucial for the antiproliferative activities.[11a]

Here, we report the hypoiodite-catalyzed tandem oxidative dearomative peroxycyclization of homotryptamine derivatives **4** to the corresponding peroxytetrahydropyridoindolenines **5** (Scheme 1c). We found that, in contrast to 5-membered peroxycyclization (Scheme 1b),[11] 6-membered intramolecular cyclization proceeded to give a tetrahydropyridoindole intermediates **7**[12] before intermolecular oxidative coupling with a peroxide to give peroxyindolenines **5**. In addition, we obtained epoxytetrahydropyridoindolenines **6** as unexpected products during the course of mechanistic studies by using TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) as an additive. This serendipitous finding prompted us to develop a chemoselective divergent synthesis of peroxy- and epoxyindolenines **5** and **6** by simple modification of the reaction conditions. Moreover, we demonstrated the synthetic utility of epoxyindolenines **6** to provide synthetically useful structures such as oxindoles, iminoester, and 2-methyleneindolenine derivative.

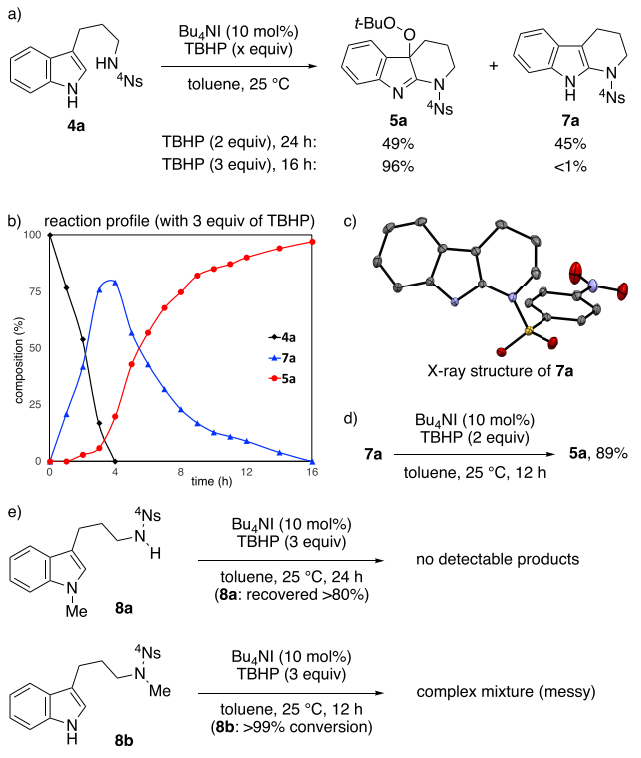
We began our investigation by examining the oxidative coupling of homotryptamine derivative **4a** using TBHP as an oxidant and coupling partner in the presence of 10 mol % of Bu_4NI (Scheme 2).[13] After an investigation of the reaction parameters (i.e., solvents, amount of oxidant used, etc.),[13] we found that a clean reaction proceeded with the use of 3 equiv of TBHP in toluene at room temperature to give the desired peroxyindolenine **5a** in 96% yield (Scheme 2a). When 2 equiv of TBHP was used, tetrahydropyridoindole **7a** was obtained in 45% yield along with **5a**. The structure of **7a** was confirmed by X-ray analysis (Scheme 2c). A reaction kinetic profile analysis using in situ ^1H NMR monitoring of the reaction progress revealed the rapid consumption of **4a** to give **7a** as an intermediate, which was then converted to **5a** via intermolecular oxidative coupling with TBHP (Scheme 2b). The intermediacy of **7a** was also confirmed by a control experiment using isolated **7a**, which was reacted with 2 equiv of TBHP under identical conditions to give **5a** in 89% yield (Scheme 2d). These results indicated that, in contrast to Zhong's oxidative 5-membered peroxycyclization under high-temperature conditions,[11] our 6-membered oxidative cyclization proceeded preferentially before intermolecular coupling with TBHP. In addition, no reactions were observed in the absence of Bu_4NI for either the aminocyclization of **4a** to **7a** or the oxidative peroxidation of **7a** to **5a**.

Because our initial findings suggested that our reaction mechanism might differ from that of Zhong et al.,[11] we further investigated the reaction mechanism of oxidative 6-membered peroxycyclization in detail. As in our previous oxidative coupling reactions,[4a,b,5,6] control experiments revealed that hypoiodite might be a catalytic active species for both the oxidative cyclization of **4a** to **7a** and the peroxidation of **7a** to **5a**.[13] In addition, to evaluate the roles of indole and sulfonamide *N*-H groups for the oxidation reactions, *N*-Me indole **8a** and *N*-Me sulfonamide **8b** were prepared and examined under the standard conditions (Scheme 2e). While, the reaction of **8a** gave no detectable products and most of the starting material **8a** was recovered, the reaction of *N*-Me sulfonamide **8b** proceeded to consuming starting materials completely, albeit to give a complex mixture of unidentified products. Therefore, similar to the previous oxidative coupling of arenols in which umpolung of arenols proceeded,[5,6] umpolung of the indole moiety through the generation of *N*-I indole intermediate might be crucial for the oxidation reaction process.

Next, we questioned whether our 6-membered peroxycyclization proceeded via a radical mechanism, as in Zhong's 5-membered radical peroxycyclization.[11] Oxidative cyclization of **4a** proceeded to give **7a** in similar yields in the presence of either 1,1-diphenylethylene (DPE) or TEMPO as a radical scavenger (Scheme 3a). On the other hand, while the use of DPE did not influence the outcome of the oxidative peroxidation of **7a** to **5a**, the use of TEMPO suppressed peroxidation but gave an unexpected product, which was determined to be epoxyindolenine **6a** (Scheme 3b). Notably, epoxyindolenine **6a** was not obtained from peroxyindolenine **5a** under identical conditions in the presence of TEMPO (Scheme 3c), suggesting that a different route may be followed from common intermediate **7a** to epoxide **6a**.

We were interested in this unexpected new reaction, and especially investigated the role of TEMPO for the epoxidation of tetrahydropyridoindole **7a** (Scheme 3d). Again, no reaction proceeded in the absence of iodide or TBHP, suggesting that both are required for oxidative epoxidation, as in peroxidation (entries 3 and 4 versus entries 1 and 2). Given the results in Scheme 3b that another radical scavenger (i.e., DPE) did not suppress the peroxidation reaction, we speculated that TEMPO might not suppress peroxidation by the scavenging

Scheme 2. Tandem Oxidative Cyclization/Peroxidation of 4a



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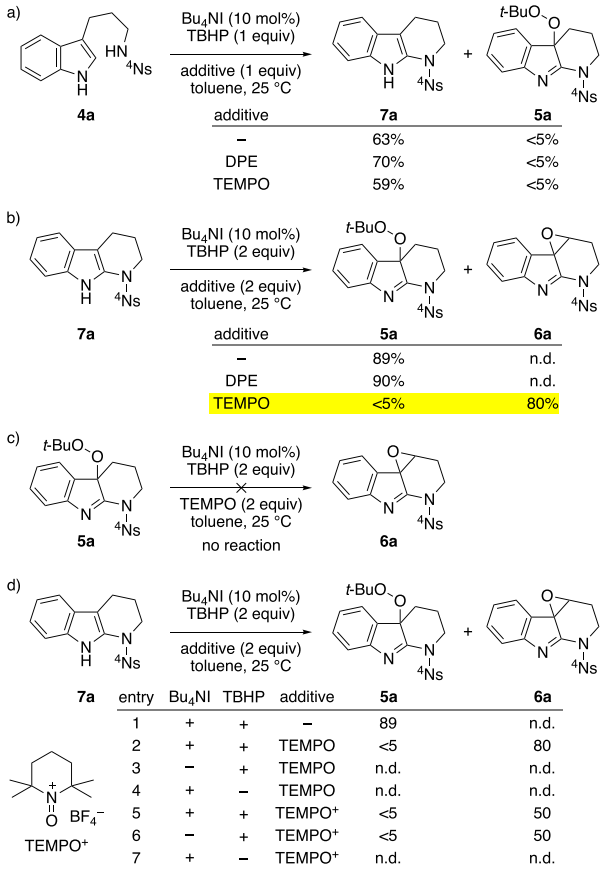
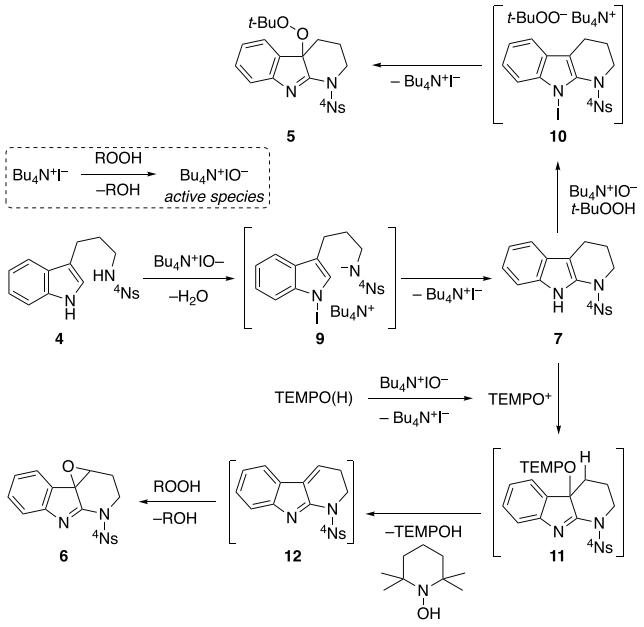
Scheme 3. Control Experiments and Serendipitous Findings



of radical species but rather might mediate epoxidation through the preferential reaction of TEMPO or its derivatives with indole **7a**. Because TEMPO could be oxidized under oxidative conditions,[14] we next investigated $TEMPO^+BF_4^-$, an oxoammonium cation, as an additive, and **6a** was obtained in 50% yield (entry 5). Notably, in sharp contrast to the result in entry 3, which confirmed the indispensability of iodide when TEMPO was used as an additive, the epoxidation of **7a** proceeded in similar efficiency in the absence of iodide catalyst when $TEMPO^+$ was used as an additive in the presence of TBHP (entry 6). These results suggested that hypoiodite might catalyze the oxidation of TEMPO to $TEMPO^+$, but is not required for the epoxidation process. In addition, the reaction of **7a** with only $TEMPO^+$ in the absence of TBHP gave a complex reaction mixture of many unidentified products and the formation of epoxide **6a** was not observed (entry 7), indicating that TBHP should be required as an oxidant for epoxidation of an unstable intermediate, which might be generated from the reaction of **7a** with $TEMPO^+$.

On the basis of the above observations and previous findings,[5,6] a proposed reaction mechanism is depicted in Scheme 4. A reversible dehydration of substrate **4** with in situ-generated ammonium hypoiodite catalytic active species might afford the indolyl hypoiodite **9** intermediate,[15,16] which might then give tetrahydropyridoindole **7** through intramolecular aminocyclization at the C-2 position.[12c] Peroxidative dearomatization might proceed via an indolyl hypoiodite species **10**,[15] which gave peroxyindolenines **5** via intermolecular S_N2' addition of ammonium *tert*-butylperoxide at the C-3 position.[6] Due to the dual role of TBHP, 3 equiv of TBHP should be required to complete the two-step reaction sequence **4** to **5**

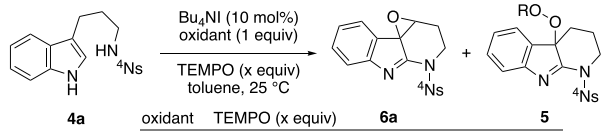
Scheme 4. Proposed Reaction Mechanism



(i.e., 2 equiv for oxidative transformation as an oxidant and 1 equiv as a peroxide source), and notably, an excellent productive usage ratio (~96%) of TBHP was observed under our mild conditions (Scheme 2a). On the other hand, in the presence of $TEMPO^+$, which would be generated in situ from the oxidation of TEMPO with hypoiodite species, electrophilic addition to **7** at the C-3 position[17] might proceed preferentially to give aminooxyindolenine **11**.[15] Elimination of TEMPOH[18] might proceed to give 3-alkylideneindolenine **12**[15] as an unstable and highly reactive intermediate,[19] which might then react with TBHP to give epoxyindolenine **6**.

An investigation of the reaction parameters for the tandem oxidative cyclization/epoxidation of **4a** to **6a** revealed that, in the presence of 1.1 equiv of TEMPO, competitive peroxidation was suppressed completely with the use of cumene hydroperoxide (CHP) as a sterically more hindered oxidant, and **6a** was obtained in 81% isolated yield (Scheme 5).[13] Importantly,

Scheme 5. Tandem Oxidative Cyclization/Epoxidation of 4a



the amount of TEMPO could be reduced to the catalytic quantities (20 mol %) to give **6a** in 67% yield (see Scheme 4 for mechanistic consideration, in which TEMPOH might be oxidized to $TEMPO^+$),[14,18] albeit with the generation of peroxyindolenine in 15% yield. Considering the chemoselectivity and efficiency, we used 1.1 equiv of TEMPO for further study. On the other hand, the use of other commercially available nitroxyl radicals such as 4-oxo-TEMPO, keto-ANBO,[20] or nor-AZADO[21] gave inferior results.[13]

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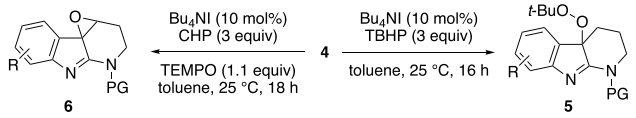
Several homotryptamine derivatives **4** were examined for tandem oxidative cyclization/peroxidation or epoxidation under the optimized conditions (Table 1).[22] Beside the 4-

Table 1. Chemoselective Divergent Oxidation to Peroxy- and Epoxyindolenines 5 and 6[a]



entry	4	PG	R	yield, 5[b] (%)	yield, 6[b] (%)
1	**4a**	^{4}Ns	H	96	81
2	**4b**	Ts	H	97	89
3	**4c**	Ms	H	56	74
4	**4d**	^{4}Ns	5-MeO	84	70
5	**4e**	^{4}Ns	5-Me	88	78
6	**4f**	^{4}Ns	7-Me	81	78
7	**4g**	^{4}Ns	4,6-Me_2	53	83
8	**4h**	^{4}Ns	5-Br	92 (92)[c]	84 (83)[c]
9	**4i**	^{4}Ns	5,7-F_2	86	82

[a]Unless otherwise noted, 0.2 mmol of **4** was used. [b]Isolated yield. [c]1 mmol of **4h** was used.

nosyl group as a protecting group for the amine tether, other sulfonyl groups such as tosyl (Ts) and methanesulfonyl (Ms) groups could also be used to afford the desired peroxides **5b** and **5c** or epoxides **6b** and **6c**, respectively (entries 2 and 3). However, peroxycyclization of **4c** yielded **5c** in only moderate yield, and several unidentified side products were also obtained. The reason for this result is not yet clear. Several electron-donating or -withdrawing group substituted indoles **4d–g** tethered to a 4-nosylamino group gave the corresponding peroxides **5** or epoxides **6** in good to high yields (entries 4–9). Notably, we confirmed the structures of two representative products **5h** and **6d** by X-ray crystallographic analysis (Figure 1).

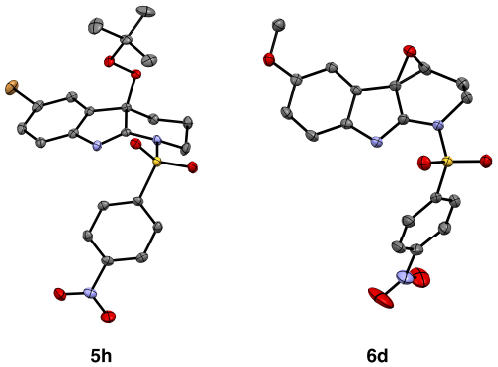
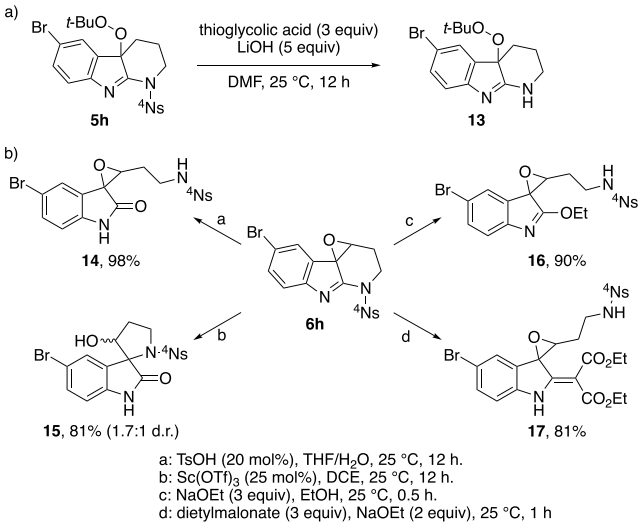


Figure 1. X-ray structures of peroxide **5h** and epoxide **6d**.

The 4-nosyl group of the peroxide adduct **5h** could be easily removed under standard deprotection conditions (Scheme 6a). The synthetic utility of peroxyindolenines and their indoline derivatives has been previously demonstrated.[11b] Here, we specifically would like to demonstrate the synthetic utility of epoxyindolenines **6** (Scheme 6b). Brønsted acid-catalyzed chemoselective opening of the tetrahydropyrido ring was accomplished under aqueous conditions to give spiroepoxyoxindole **14** as a synthetically highly useful compound.[23] In

Scheme 6. Transformation of Peroxy- and Epoxyindolenines



addition, tandem ring-opening/recyclization of tetrahydropyrido and oxirane rings proceeded to give a diastereomeric mixture of 3,3-spiropyrrolooxindole **15** in good yield when $Sc(OTf)_3$ was used as a Lewis acid catalyst. On the other hand, opening of the tetrahydropyrido ring also proceeded smoothly with an alkoxide to give iminoester **16**. Moreover, C–C bond formation with malonate under basic conditions could also trigger ring-opening to give spiroepoxyindoline-2-ylidenemalonate **17** in good yield.

In summary, we developed the hypoiodite-catalyzed tandem oxidative dearomative peroxycyclization of homotryptamine derivatives to the corresponding peroxytetrahydropyridoindolenines. We found that, in contrast to the previously reported 5-membered peroxycyclization,[11] 6-membered intramolecular cyclization proceeded to give tetrahydropyridoindole intermediates before intermolecular oxidative coupling with a peroxide to give peroxyindolenines. More importantly, we obtained epoxytetrahydropyridoindolenines as unexpected but synthetically useful products during the course of mechanistic studies using TEMPO as an additive. While oxidative coupling with TBHP at C-3 position might afford peroxyindolenines, a preferential electrophilic addition of $TEMPO^+$, which might be generated in situ by the hypoiodite-catalyzed oxidation of TEMPO, at C-3 position followed by elimination and epoxidation might give epoxyindolenines. This serendipitous finding prompted us to develop a chemoselective divergent synthesis of peroxy- and epoxyindolenines and by simple modification of the reaction conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03001.

Additional information, experimental procedures, characterization of new compounds, and spectral data (PDF)

Accession Codes

CCDC 2028556, 2028585, and 2028607 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data

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Notes

The authors declare no competing financial interest.

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