Collective asymmetric synthesis of the *Strychnos* alkaloids via thiophene *S,S*-dioxide cycloaddition cascades

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Summary Paragraph: The *Strychnos* alkaloids have long been regarded as landmark targets for chemical synthesis due to their captivating architectures and notorious biological properties. The family has fascinated synthetic and medicinal chemists for almost 100 years, since the decades-long debate over the structure of the 'flagship' member strychnine[1], and its first total synthesis by Woodward[2]. Featuring a dense array of carbo- and heterocyclic rings, and numerous stereochemical challenges, these molecules have inspired many synthetic strategies[3,4]. In spite of this rich history, the design of approaches that can access multiple family members, in an asymmetric, concise, and atom-economical fashion, remains a significant challenge. Here we show that thiophene *S,S*-dioxides (TDOs) offer a modular and highly concise entry to the *Strychnos* natural products. We show how the rapid assembly of a tryptamine-tethered TDO enables the synthesis of family member akuammicine in just three steps from tryptamine, with minimal waste generation. We further demonstrate exceptional levels of stereocontrol in unprecedented asymmetric cycloadditions of chiral thiophene *S,S*-dioxides; these afford tricyclic indolines that are of interest for medicinal chemistry applications, and also enable highly concise, stereoselective and scalable syntheses of the *Strychnos* alkaloids by either intra- or intermolecular asymmetric cycloadditions. Our results highlight the

potential of TDOs as important building blocks in asymmetric cycloaddition chemistry for the streamlined synthesis of polycyclic organic frameworks; in the case of the *Strychnos* alkaloids, this means that both natural products and analogues that have previously been inaccessible can now be prepared in a handful of transformations.

Main Text: The *Strychnos* indole alkaloid natural products have long excited the synthetic and medicinal chemistry community due to their potent biological properties and unique architectural complexity (Fig. 1a). The flagship member of this family – strychnine – was infamously described by Robinson that 'for its molecular size, it is the most complex substance known'[1], with its biosynthesis only recently having been elucidated[5]. The landmark synthesis of this natural product by Woodward[2,6] inspired decades of synthetic creativity, and the invention of many approaches to the *Strychnos* family[3,4,7]. In addition to the structural challenges, these endeavours have also been inspired by potential biological applications, such as the identification of alstolucines B and F as candidates for resensitisation of taxanes in multidrug-resistant cancers[8]. However, synthetic approaches that are sufficiently concise to produce useful quantities of natural product, but also sufficiently flexible to enable the 'collective' synthesis of multiple family members, are rare. Additional demands of 'synthesis ideality'[9], such as the avoidance of protecting groups and the minimisation of waste (i.e. atom economy)[10], whilst also achieving enantioselectivity, impose further challenges that limit the wider exploitation of the *Strychnos* alkaloids in biological settings. In this context, the six step racemic synthesis of strychnine by the Vanderwal group[11] and the collective asymmetric synthesis of six indole alkaloids by MacMillan *et al.* (including a 12 step approach to strychnine)[12] represent pioneering contributions, with recent elegant approaches also having been described by the Zhang[13] and Snaddon[14] groups.

We questioned whether a new entry to the *Strychnos* family might be designed that could meet the stringent demands of contemporary synthetic chemistry. We envisioned a modular strategy that would

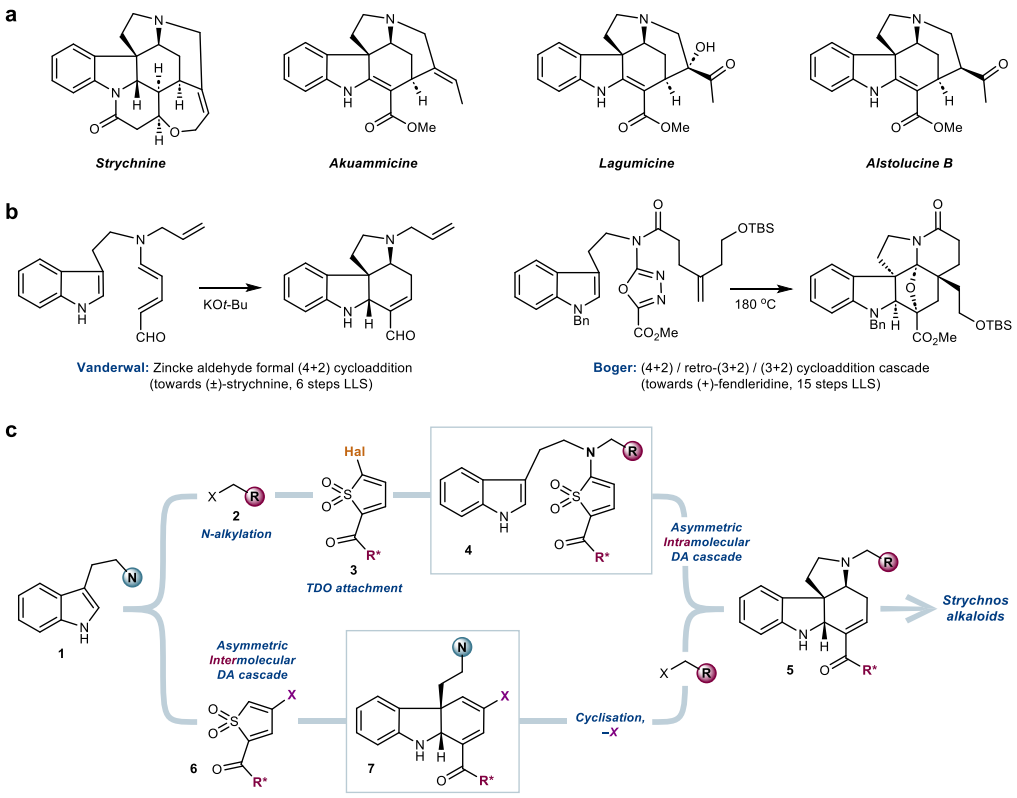

Fig. 1. Representative *Strychnos* alkaloids, selected previous cycloaddition approaches to indole alkaloids, and the synthesis blueprint in this work. a, Examples of *Strychnos* alkaloids include strychnine, akuammicine, lagumicine and alstolucine B. **b,** Previous inverse electron-demand cycloaddition approaches to indole alkaloids include the use of Zincke aldehydes and oxadiazoles. **c,** This work, in which two modular strategies are explored to access tetracycle **5**, a key precursor for the collective synthesis of eight *Strychnos* alkaloids, *via* asymmetric cycloaddition cascades of thiophene *S*,*S*-dioxides (TDOs). R* depicts a chiral substituent.

enable the enantioselective construction of the *Strychnos* core in a handful of steps, and therefore access multiple natural products in a scalable and procedurally straightforward manner whilst also minimising the generation of undesirable waste byproducts. In considering possible approaches, we recognised that the indoline core of the alkaloids is an attractive motif for ring formation *via* cycloaddition, in which an indole precursor would serve as an electron-rich 2π component. This concept has been exploited by Vanderwal (*via* formal inverse-electron demand Diels-Alder (IEDDA)

cycloadditions with tethered Zincke aldehydes, Fig. 1b)[11,15], and also the Boger and Padwa groups (*via* (3+2) cycloadditions with tethered carbonyl ylides)[16,17]; Padwa *et al.* also reported a (4+2) cycloaddition using a tethered aminofuran in a racemic synthesis of strychnine[18]. However, these elegant strategies also suffer from drawbacks, such as the need for prolonged heating when employing aromatic cycloaddition partners (i.e. furans, oxadiazoles), or the use of diazo compounds and transition metal catalysts (for carbonyl ylide synthesis), or in affording racemic natural products.

We recognised that thiophene *S,S*-dioxides (TDOs)[19] could address such limitations, as these heterocycles are in many ways 'ideal' diene substrates for IEDDA reactions. In contrast to oxadiazoles and other well-explored IEDDA substrates such as pyrones and tetrazines, TDOs are non-aromatic and therefore exhibit enhanced reactivity, while retaining the benefits of electron deficiency, an intrinsically *s-cis* constrained diene, and a powerful entropic driving force that renders the cycloaddition irreversible (namely, loss of SO_2 through cheletropic extrusion). The deployment of TDOs in target-oriented synthesis remains surprisingly rare[20,21], but encouraged by our recent study[22] in the context of the illudalane sesquiterpenes, we contemplated their application in the construction of the *Strychnos* alkaloids. Deviating from previous examples where TDOs have been used in the *de novo* construction of polysubstituted benzenes[20-24], we questioned whether these underexploited dienes could also be used to assemble the non-aromatic carbocyclic *Strychnos* core. No asymmetric TDO cycloadditions have been described to date, and we further considered whether we might not only use these easy-to-access heterocycles in a concise synthesis of a number of the *Strychnos* alkaloids, but also simultaneously develop the first asymmetric cycloadditions of TDOs, which would render this collective synthesis enantioselective.

In considering strategies to achieve these goals, we recognised that two approaches might afford access to the *Strychnos* core (Fig. 1c). We first envisaged that tryptamine (**1**) could undergo alkylation with a sidechain (**2**) suitable for downstream completion of the targeted natural products, and then an addition-elimination (substitution) reaction with a halogenated thiophene *S,S*-dioxide **3** to give intermediate **4**. This TDO would react with the tethered indole *via* a stereoselective intramolecular

IEDDA / SO_2 cheletropic extrusion pathway to form tetracycle **5** after reduction of the intermediate cycloadduct, further functionalisation of which would afford the *Strychnos* natural products. Alternatively, we considered an *inter*molecular Diels-Alder approach, in which a tryptamine derivative **1** would undergo direct cycloaddition with TDO **6** to form adduct **7**. **6** would necessarily feature a disposable substituent ('X') that is essential to prevent heterodimerisation of the thiophene *S*-monoxide with *S,S*-dioxide **6** in the course of its oxidative synthesis[19]. Subsequent to the cycloaddition / cheletropic extrusion cascade, cyclisation of the tryptamine sidechain, cleavage of the now superfluous substituent 'X', and *N*-alkylation with **2** would afford the same advanced intermediate **5**. Here we describe the development of these two strategies, culminating in a collective asymmetric synthesis of eight natural products in the *Strychnos* family. In doing so, we also establish the first asymmetric intermolecular cycloadditions of TDOs, accessing tricyclic indoline scaffolds that are of potential utility for medicinal chemistry applications. We further use computational studies to reveal the source of the exquisite stereoselectivity observed in the IEDDA reaction, which also suggest that these TDO cycloadditions benefit from an entropic driving force where cheletropic extrusion of SO_2 occurs spontaneously along the cycloaddition pathway, without formation of an intermediate cycloadduct.

The feasibility of the proposed intramolecular cascade was first tested in the setting of a racemic synthesis of akuammicine (Fig. 2a). The required thiophene *S,S*-dioxide **8** was synthesised from the corresponding commercially-available 2-chlorothiophene ester *via* peroxyacid oxidation[25], while the synthesis of the indole dienophile **9** involved a simple *N*-alkylation of tryptamine with known sidechain **10** (prepared in two steps)[26]. With these building blocks in hand, the key halide substitution / intramolecular cycloaddition / cheletropic extrusion cascade was investigated. Reaction of TDO **8** with amine **9** at room temperature, followed by warming to 75 °C, efficiently furnished the cycloaddition cascade product **11**. Reduction of the enamine in **11** proved challenging; the combination of acetic acid and sodium cyanoborohydride at 65 °C was found to afford the desired diastereomer **12** and its epimer **12'** in 63% overall yield (1:2.4 *dr*), in favour of **12'**[27,28]. The adverse

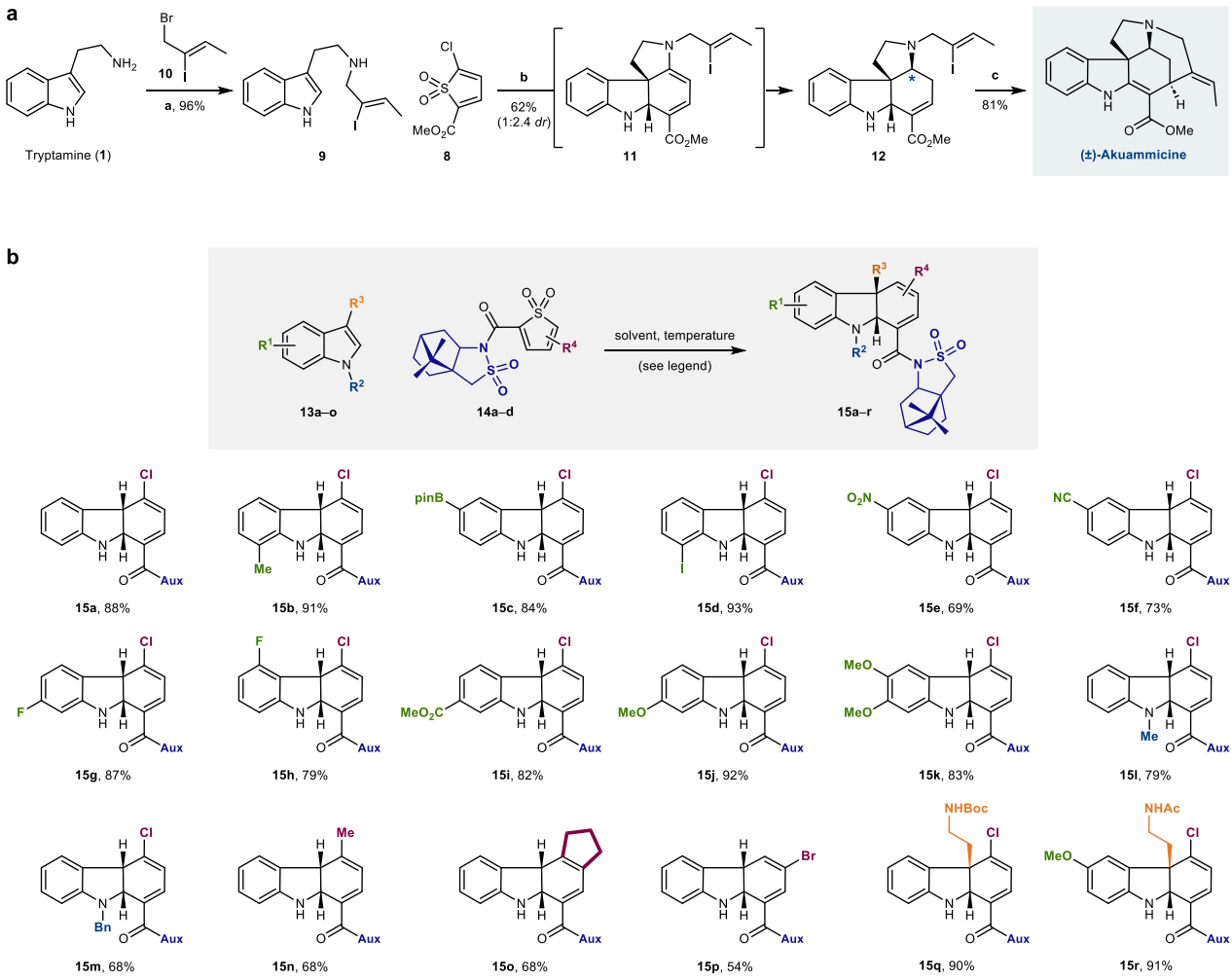

Fig. 2. Development of stereoselective TDO cycloadditions. a, A three step synthesis of (±)-akuammicine from tryptamine. a) MeCN, r.t.; b) MeCN, r.t. to 75 °C; then AcOH, $NaBH_3CN$, 65 °C; c) $Pd(OAc)_2$, PPh_3, Et_3N, 70 °C. **b,** Stereoselective intermolecular cycloadditions using indoles (2.0 equiv.) and enantiopure camphorsultam-substituted thiophene *S*,*S*-dioxides (1.0 equiv.) in CH_2Cl_2 at 0 °C. The synthesis of **15e** and **15i** was carried out at room temperature. The synthesis of **15q** and **15r** was carried out at 80 °C in $CHCl_3$.

selectivity of this step likely derives from the preferred delivery of hydride to the less-hindered concave face of the intermediate iminium ion. We nonetheless found that this three step sequence could be streamlined by performing the enamine reduction in the same reaction flask immediately after the cycloaddition, such that the synthesis of **12/12'** could be achieved in 62% combined yield

from **9**. An intramolecular Heck reaction[29,30] of the desired isomer **12** (81%) completed the synthesis of akuammicine in three steps from tryptamine (five steps in the longest linear sequence (LLS) that includes assembly of the sidechain **10**). This route represents the most concise assembly of (±)-akuammicine to date and, aside from the use of organic solvents, also avoids the formation of any carbon-containing waste.

With the feasibility of the synthesis established, we next addressed the development of hitherto unrealised asymmetric TDO cycloadditions. Investigations began with intermolecular (4+2) cycloadditions between indoles and enantioenriched thiophene *S,S*-dioxides equipped with inexpensive, readily available chiral substituents. We were delighted to find that reaction of indole (**13a**) with a TDO substituted with an acyl camphorsultam group[31] (**14a**, R^4 = 5-Cl) in CH_2Cl_2 at 0 °C afforded tricycle **15a** as a single diastereoisomer in high yield. This method was tested on a range of substituted indoles, and showed broad functional group tolerance of both electron rich (e.g. methoxy) and electron poor substituents (e.g. ester, nitro, nitrile) at various positions around the indole ring, as well as useful functionality such as boronic esters and halides. *N*-substitution was also accommodated, with all tricyclic products isolated as single diastereomers in good to excellent yields (**15b**-**15m**, 68-93%). Variation of the thiophene *S,S*-dioxide was also well-tolerated, including a bicyclic TDO (**15n**-**15p**, 54-68%). With a view towards the proposed intermolecular cycloaddition approach to the *Strychnos* alkaloids, we further evaluated the use of 3-substituted indoles in this chemistry. Pleasingly, these reactions were also successful, albeit requiring higher temperatures to effect the cycloaddition due to the steric demand imposed by the additional indole substituent, affording cycloadducts **15q** and **15r** in 90% and 91% yields respectively, again as single diastereomers.

With highly selective, asymmetric intermolecular TDO cycloadditions established, we turned to enantioselective syntheses of the *Strychnos* alkaloids. We first explored the asymmetric variant of the intramolecular (tethered) cascade already established for the racemic synthesis of akuammicine (see Fig. 2a); a key issue was whether the excellent stereocontrol imparted by the camphorsultam group

for the intermolecular cycloadditions would be maintained in an intramolecular setting. To our delight (Fig. 3a), treatment of the *N*-alkylated tryptamine **9** with TDO **14a** under equivalent conditions to those employed previously (r.t. to 80 °C) afforded a single diastereoisomer of the IEDDA cycloadduct; this intermediate dienamine was also reduced *in situ* to afford two isomers **16** and **16'** in a 1:1.4 ratio (see Supplementary Table S1 for details) and 68% overall yield from **14a**.

In spite of the concise nature of this synthetic sequence, the poor selectivity again observed in the reduction of the initially formed dienamine cycloadduct prompted us to consider the alternative intermolecular asymmetric cycloaddition strategy. We identified 4-bromo-TDO **14d** (as used in the synthesis of **15p**, Fig. 2b) as a potential candidate for this route, since its bromine substituent would protect the corresponding thiophene from unwanted dimerisation during oxidation[19] and could also likely be removed under mild conditions later in the synthesis. We were pleased to find that the intermolecular cycloaddition of *N*-Boc tryptamine **17** with **14d** (used directly from oxidation of thiophene **18**) afforded a single diastereomer of dihydrocarbazole **19**. *In situ* addition of trifluoroacetic acid effected Boc deprotection and triggered cyclisation of the tryptamine sidechain onto the dienoyl motif, giving a single diastereomer of the pyrrolidine product **20** in 57% yield (from **18**) after a basic workup. We found that the allylic bromide resident in **20** could then be selectively cleaved by hydrogenolysis without reduction of the adjacent alkene; attachment of the vinyl iodide sidechain **10** smoothly afforded **16**, thus intercepting the intramolecular cycloaddition route, but now with perfect control of stereochemistry at the three contiguous stereocentres within the tetracycle. To complete the asymmetric synthesis of akuammicine, the camphorsultam amide underwent methanolysis[32] to the corresponding ester **(–)-12** (67%), with the camphorsultam moiety recovered in high yield. Heck cyclisation of **(–)-12** proceeded in 75% yield to afford (–)-akuammicine. This synthesis proceeded in six steps in the longest linear sequence (LLS) by the intramolecular cycloaddition route (or just four steps from tryptamine, 14% overall yield), or in seven steps LLS *via* the intermolecular variant (20% overall yield). Four additional natural products (lagumicine, alstolucines B and F, and echitamidine) were synthesised from akuammicine using an established

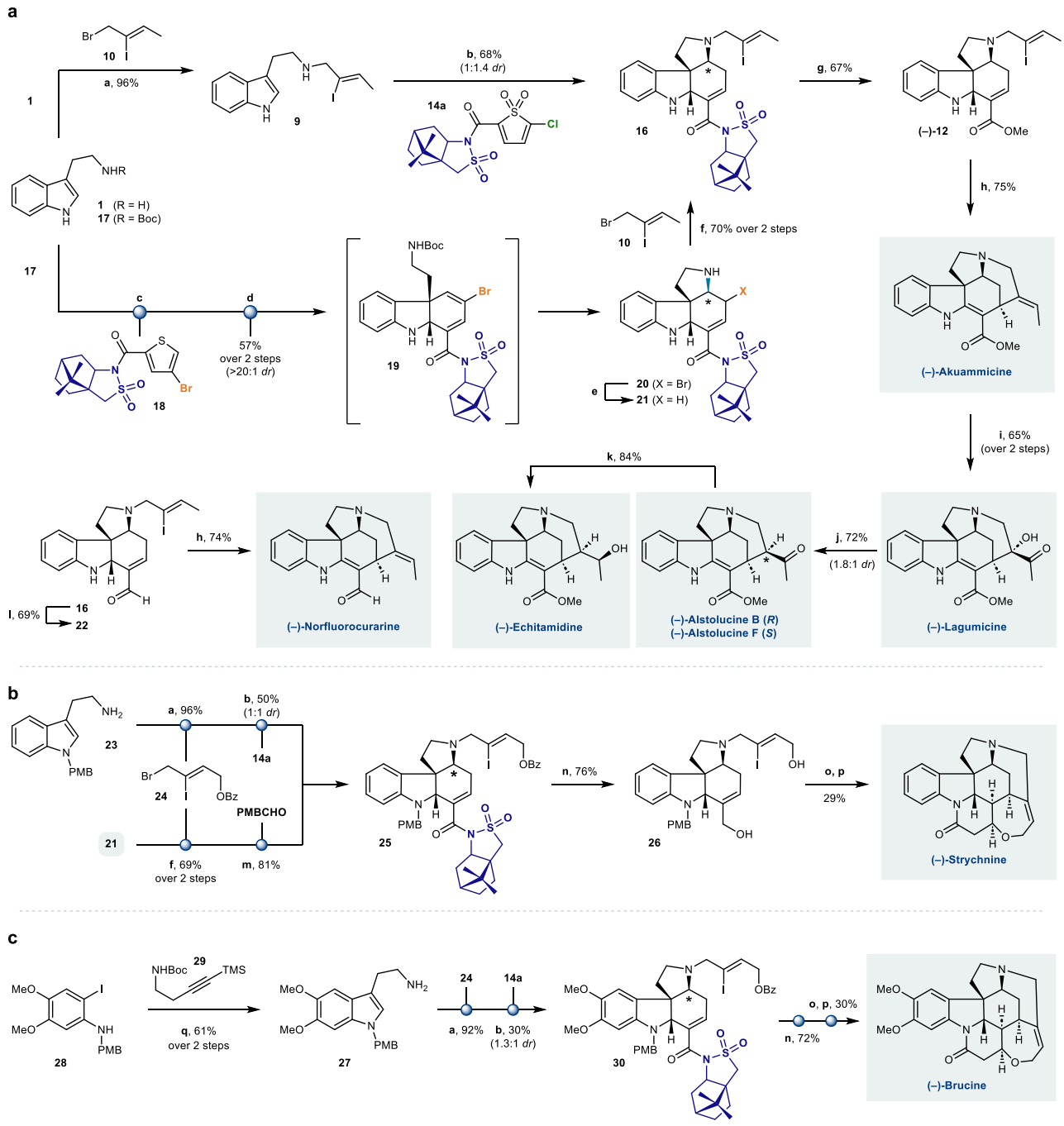

Fig. 3. Collective asymmetric syntheses of *Strychnos* alkaloids. a, Syntheses of akuammicine, norfluorocurarine, lagumicine, alstolucines B and F, and echitamidine, **b,** Synthesis of strychnine, **c**, Synthesis of brucine. Reagents and conditions are as follows. a) MeCN, r.t.; b) MeCN, r.t. to 80 °C (70 °C for **30**); then AcOH, $NaBH_3CN$, 65 °C (55 °C for **30**); c) TFAA, H_2O_2, 0 °C to r.t.; d) **17**, $CHCl_3$, 80 °C; CF_3COOH, CH_2Cl_2, r.t.; e) H_2 (1 atm.), Pd/C, MeOH:EtOAc, r.t.; f) Na_2CO_3, MeCN, r.t.; g) NaOMe, dimethyl carbonate, CH_2Cl_2, 0 °C; h) $Pd(OAc)_2$, PPh_3, Et_3N, 70 °C; i) $K_2OsO_4•2H_2O$, $NMO•H_2O$, *t*-BuOH:H_2O, r.t.; then Dess-Martin periodinane, ^{t}BuOH, CH_2Cl_2, r.t.; j) SmI_2,

THF:MeOH, 0 °C to r.t.; k) $NaBH_4$, MeOH, 0 °C to r.t.; l) DIBALH, CH_2Cl_2, -78 °C; m) *p*-anisaldehyde, $NaBH(OAc)_3$, AcOH, DCE, 0 °C to r.t.; n) DIBALH, CH_2Cl_2, -78 to 0 °C; o) $Pd(OAc)_2$, Bu_4NCl, $NaHCO_3$, EtOAc, r.t.; p) PhSH, TFA, 45 °C (50 °C for brucine); then NaOAc, Ac_2O, AcOH, malonic acid, 120 °C; q) $Pd(OAc)_2$, LiCl, K_2CO_3, DMF, 105 °C; then CSA, ^{i}PrOH, 50 °C.

sequence[33], while (–)-norfluorocurarine was prepared from **16** by initial reduction to aldehyde **22** with DIBALH (69%) followed by Heck cyclisation (74%).

We next turned our attention to strychnine, which necessitated use of PMB-protected tryptamine **23** (Fig. 3b) in order to ensure correct regioselectivity in the endgame Heck cyclisation[12]. Once again, both intra- and intermolecular strategies were evaluated. In the intramolecular context, **23** underwent smooth alkylation with sidechain **24** (96%), followed by the cyclisation cascade with TDO **14a**. As before, a single diastereomer of the diene cycloadduct was observed, which following *in situ* reduction gave the tetracyclic product **25** in 50% overall yield (1:1 *dr*) over two steps. Pleasingly, we found that the intermolecular approach again offered superior selectivity, at a cost of one additional synthetic step: Alkylation of **21** (employed in the akuammicine synthesis) with sidechain **24** (69% from **20**) followed by PMB protection of the indoline nitrogen atom (81%) gave tetracycle **25**. From here, exhaustive reduction with DIBALH afforded diol **26** (76%), Jeffery–Heck cyclisation/lactol formation from which proceeded smoothly to afford the PMB-protected Wieland–Gumlich aldehyde (57% yield). This was converted to (–)-strychnine *via* deprotection of the PMB group, followed by treatment with malonic acid, acetic anhydride and sodium acetate (50% over two steps).[12] This asymmetric synthesis of the natural product was thus completed in seven steps from tryptamine (nine steps LLS including synthesis of sidechain **24**) *via* the intramolecular route, while the intermolecular variant entailed a ten step LLS, representing the most concise asymmetric approach reported to date.

Despite the rich history of the *Strychnos* alkaloids, there is one family member that has thus far eluded chemical synthesis: brucine. This dimethoxy analogue of strychnine has been known for over 200

years, and has been employed by chemists as a chiral resolving agent since Fischer's seminal report in 1899[34]; its catechol derivative has been exploited as a chiral ligand in asymmetric catalysis[35]. The challenge for any synthesis of brucine relates to the highly electron-rich nature of the indoline ring, which confers sensitivity towards oxidation and electrophilic degradation. To implement the TDO cascade approach to brucine, we first needed to synthesise *N*-PMB-5,6-dimethoxytryptamine **27**. Due to the aforementioned instability of electron-rich aromatics, precedents for the synthesis of highly oxidised tryptamines are not well documented, but after extensive investigation we found that **27** could be accessed using a Larock indole synthesis[36,37] between iodoaniline **28** and alkyne **29**, which afforded **27** in good yield (61% over two steps). The successful progression of **27** towards brucine *via* the intramolecular cascade required only minor modifications to the route employed for strychnine: alkylation of **27** with sidechain **24** proceeded uneventfully (92%), but due to the reduced stability of the 5,6-dimethoxyindole, the intramolecular TDO cascade with **14a** required a lower reaction temperature (60 °C) with a correspondingly longer reaction time in order to prevent decomposition, affording product **30** after reduction of the dienamine (30% yield from **27**, 1.3:1 *dr*). An endgame sequence of DIBALH-mediated benzoate reduction / sultam cleavage (72%), Heck cyclisation / lactolisation (57%), and finally PMB deprotection and malonic acid condensation, accomplished the first total asymmetric synthesis of (–)-brucine (9 steps LLS from commercial 2-iodo-4,5-dimethoxyaniline). Attempts to implement the alternative intermolecular cascade proved unfruitful, with complex mixtures observed under the cycloaddition conditions, presumably reflecting the challenge of deploying a highly electron-rich indole.

To better understand the basis of the remarkable levels of asymmetric induction imparted by the TDO camphorsultam sidechain, we turned to computational modelling. Quantum mechanics (QM) calculations and molecular dynamics simulations driven by machine learning potentials (MLPs) were performed to model the cycloaddition step. MLPs "learn" the high-dimensional potential energy surfaces (PES) from QM calculations, effectively mapping atomic positions to energies and, often, forces with accuracy comparable to QM and efficiency comparable to simple empirical force fields[38].

We initially investigated the conformational preference of the camphorsultam group relative to the TDO ring using the simplified TDO **31**, featuring a C5-dimethylamine substituent (Fig. 4). In the lowest energy conformer **A**, the C2 carbonyl group is oriented *syn* to the TDO sulfone, with the C=O bond bisecting the two S=O bonds. This arrangement allows for coplanarity between the carbonyl and the TDO ring, and maximises conjugation with the C5 amine nitrogen atom, with the sultam N–S bond positioned *anti*- to the carbonyl group to minimize steric clash with the TDO ring. To investigate preference for conformer **A**, a 2D energy profile was constructed, as a function of the torsion angles around the (TDO)C–C(=O)(β) and C(=O)–N(sultam)(α) bonds, using an MLP trained at the CPCM(MeCN)-B2PLYP-D3BJ/def2-SVP level of theory, which enabled efficient sampling of the PES (details of the training of MLPs are presented in Sections 4.1 and 4.4 of the Supplementary

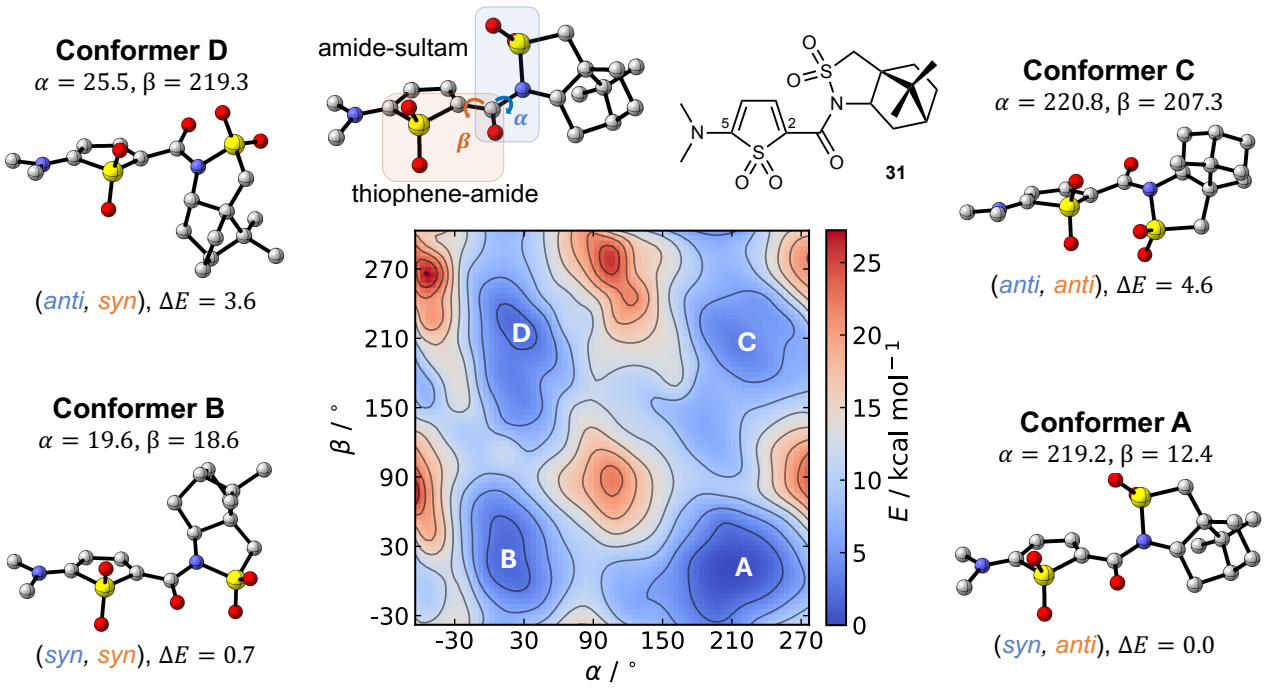

Fig. 4. Conformational analysis of the camphorsultam-substituted TDO 31. 2D energy profile (kcal mol^{-1}) as a function of torsion angles around the C–C and C–N bonds flanking the carbonyl generated using a machine learning potential (MLP) trained at CPCM (MeCN)-B2PLYP-D3BJ/def2-SVP level of theory using the MACE architecture.[39,40] Each minimum was further characterised at the CPCM(MeCN)-DLPNO-CCSD(T)/def2-TZVP//CPCM(MeCN)-B2PLYP-D3BJ/def2-SVP level of theory (353 K / 1 M).

Information). The next highest energy minimum is Conformer **B**, which lies 0.7 kcal mol^{-1} higher in energy, in which the amide-sultam C–N bond is rotated ~180° relative to **A**. Conformer **B** benefits from enhanced $n_{N(sultam)} \rightarrow \pi^*_{CO}$ interaction, but at a cost of increased steric clash between the camphorsultam carbocycle and the TDO ring, which also prohibits productive cycloaddition via this conformation (see Figure S4).

To elucidate the origin of the facial selectivity (and hence the stereoinduction) of the intramolecular cycloaddition reaction, we next investigated the reaction mechanism for a model TDO **32** featuring a methyltryptamine sidechain appended to the camphorsultam-substituted TDO ring (Fig. 5a). The lowest energy conformer **I** is stabilised by a hydrogen bond between the indole NH and one of the oxygen atoms of the camphorsultam. In contrast, for the lowest energy conformer associated with reaction of the indole on the opposite face of the TDO (conformer **II**, ΔG^0 = +0.34 kcal mol^{-1}) this hydrogen bond stabilisation is not possible.

We then investigated the cycloaddition pathway from each of these conformers. For conformer **I**, we were unable to locate a concerted (4+2) transition state. Instead, the reaction follows a 'stepwise' mechanism, where only the bond between C3 of the indole and C5 of the TDO ring (r_1^{CC}) is formed at **TS I** ($\Delta G^{\ddagger}$ = 26.5 kcal mol^{-1}); the second C–C bond (r_2^{CC}) cannot be formed due to steric clash between the camphorsultam and the indole ring, leading to the high energy adduct **III** (ΔG = 24.4 kcal mol^{-1}). However, for conformer **II**, a concerted, asynchronous (4+2) mechanism was found, which proceeds via **TS II** ($\Delta G^{\ddagger}$ = 23.1 kcal mol^{-1}); this is followed by the unexpected, spontaneous extrusion of SO_2 to form the dienamine product **IV**. Attempts to locate the sulfur-bridged (4+2) cycloadduct where unsuccessful. This pathway, which leads to the experimentally observed product, is 3.1 kcal mol^{-1} lower in energy than the stepwise mechanism.

We explored the dynamics of the (4+2) mechanism through downhill molecular dynamics (MD) simulations using an MLP (Fig. 5b, see details in Section 4.6 of the Supplementary Information). For this study, 500 trajectories were initialised from **TS II** at 353 K and propagated downhill for five

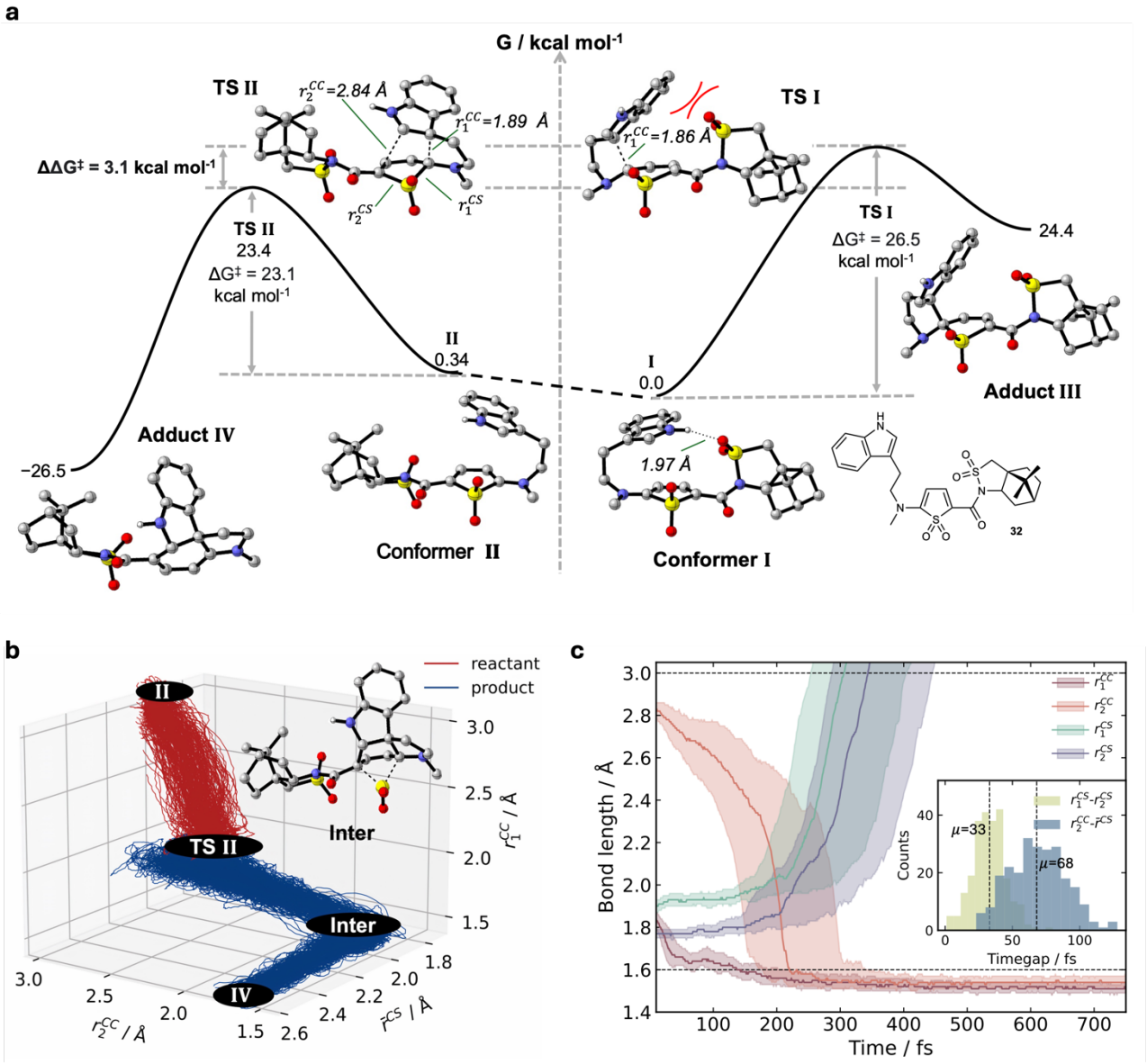

Fig. 5. Computational exploration of the intramolecular IEDDA cycloaddition of *N*-methyltryptamine-derived TDO 32. a, (4+2) Cycloaddition of the TDO with a tethered indole proceeds under Curtin-Hammett control, with only conformation **II** able to react via an asynchronous, concerted cycloaddition **TS II**. Energy profiles computed at the CPCM(MeCN)-DLPNO-CCSD(T)/def2-TZVP//CPCM(MeCN)-B2PLYP-D3BJ/def2-SVP level of theory (353 K / 1 M). **b,** Machine Learning Potential-Molecular Dynamics simulations (MLP-MD) reveal a concerted asynchronous (4+2) process, involving a short-lived intermediate (**Inter**) and spontaneous SO_2 extrusion. **c,** Time evolution of C–C and C–S distances shows the dynamic, stepwise nature of the (4+2) stage and dynamic concerted SO_2 extrusion.

picoseconds. These trajectories revealed a highly asynchronous process, with one C–C bond significantly advanced in the **TS II** region (r_1^{CC} ~1.9 Å) relative to the other (r_2^{CC} ~2.8 Å). A transient sulfur-bridged (4+2) cycloadduct (**Inter**) is observed, where the C–S bonds remain intact. As the system progresses toward the product state the C–S bonds elongate.

This asynchronicity is also evidenced in the time evolution of the relevant C–C and C–S distances (Fig. 5c, t=0 being **TS II**). The average time gap between the formation of the two C–C bonds (defined as bond lengths <1.6 Å) is 256±218 fs (ranging from 56–1804 fs), indicative of a dynamic stepwise mechanism for the (4+2) process.[41] At around 200 fs, as the second C–C bond starts to form (r_2^{CC} shortening to 1.6 Å), the C–S bonds begin to elongate, with r_1^{CS} lengthening more than r_2^{CS}. The time gap between the cleavage of the C–S bonds averages 33±12 fs (ranging from 6–80 fs); this elongation continues until SO_2 is extruded. The significant entropic driving force provided by this process likely results in lowering of the energy of **TS II** compared to the alternative stepwise cycloaddition / extrusion pathway (**TS I**), and may also guide the exclusive formation of a single diastereomer of the indoline product. In summary, only **TS II** allows a dynamic stepwise attack of the indole unit, leading to the experimental observed diastereomer (*R,S*)-adduct **IV**. Key to this selectivity is the intrinsic energetic stabilisation of the concerted pathway concomitant with a dynamic SO_2 extrusion, in combination with conformational rigidity of the camphorsultam auxiliary preventing concerted cycloaddition on the opposite face of the TDO.

Thiophene *S,S*-dioxides have rarely been exploited in synthetic contexts, but here are shown not only to offer efficient, stereoselective and general access to polycyclic indolines, but also to enable enantioselective syntheses of eight *Strychnos* alkaloids via the most concise routes reported to date. Combined with computational insight into the source and nature of conformation and cycloaddition pathways, these motifs show clear potential for broad application of thiophene *S,S*-dioxides across synthetic and medicinal chemistry.

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Author contribution

E.A.A., K.P. and J.P. conceived the project. Experimental work was carried out by K.P. and J.P.. N.F., H.Z. and F.D. carried out the computational analysis. The project was supervised by E.A.A. and F.D.. E.A.A., K.P. and N.F. wrote the initial manuscript which was reviewed and edited by all authors.

Competing interest declaration

The authors declare no competing interests.

Additional information

Supplementary Information is available for this paper.

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