Total Synthesis of Dimeric HPI Alkaloids

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Abstract In this paper, we report a full account of the synthesis of dimeric hexahydropyrroloindole alkaloids and its analogues. The key feature of our new strategy is the novel catalytic copper (10%) mediated intramolecular arylations of o-haloanilides followed by intermolecular oxidative dimerization of the resulting oxindoles in one pot. This sequential reaction leads to the key intermediates for the synthesis of (+)-chimonanthine, (+)-folicanthe, (−)-calycanthine and (−)-ditryptrophenaline.

Graphical Abstract In the presence of catalytic amount of cuprous iodide (10%), an intramolecular arylation of o-haloanilides followed by an intermolecular oxidative dimerization of the resulting oxindoles leads to a common intermediate for the synthesis of (+)-chimonanthine, (+)-folicanthe and (−)-calycanthine. Based on this cascade sequence, we also developed a flexible strategy towards the asymmetric syntheses of dimeric HPI alkaloids (−)-ditryptrophenaline and its analogues.

Keywords Copper catalyzed reaction · Oxidative dimerization · Total synthesis · Hexahydropyrroloindole · Alkaloids

1 Introduction

The hexahydropyrroloindole (HPI) structure-unit presents in a large class of natural products isolated from plants, microorganisms and fungi (for selected reviews and book chapters, see: [1–8]). Representative natural product of this family is phystostigmine (Fig. 1, 1) which was isolated from the seeds of the calabar bean plant and is currently used to treat myasthenia gravis, glaucoma, Alzheimers disease, delayed gastric emptying and orthostatic hypotension [5, 7]. There are a number of alkaloids containing more than one HPI unit and...
some of them contain a unique vicinal C3α–C3α′ quaternary carbon center [1, 4]. The stereocontrol synthesis of the congested all-carbon quaternary stereocenters in these alkaloids presents a formidable challenge [9–16]. In 1999, Overman and his team completed the first enantioselective synthesis of dimeric alkaloid (+)-calycanthine (Fig. 1, 4) and (−)-chimonanthine (Fig. 1, 2) [17]. Utilization of the same strategy, they also successfully synthesized a number of other dimeric and oligomeric HPI alkaloids [17–27]. In 2007, Mavassaggi reported a reductive radical dimerization strategy for the syntheses of dimeric HPI alkaloids (Fig. 1) [28, 29]. Based on this reductive dimerization reaction, a number of important works have been published towards the syntheses of dimeric HPI alkaloids (for selected syntheses of dimeric HPI alkaloids employed Movassaggi’s reductive dimerization, see: [30–37]). Prompted by the success of reductive dimerization strategies, studies on the oxidative dimerization of tryptamine and tryptophan derivatives have been revived and syntheses of natural HPI alkaloids, especially chimonanthine, folicanthine and ditryptophenaline, have been achieved by a number of research groups (oxidative dimerization of tryptamine and tryptophan derivatives as the key steps for the syntheses of dimeric HPI compounds before 2007: [38–58]).

Careful examination of literature related to the total syntheses of dimeric HPI alkaloids, we found that tryptamine or tryptophan derivatives were used frequently as starting materials [38–58], few examples had been documented by application of non-indole and/or non-oxindole starting materials [59]. To some extent, utilization of tryptamine and tryptophan derivatives as starting materials might limited the access of structurally diverse dimeric analogues. Therefore, it is of importance to develop alternative approaches towards the synthesis of the target dimeric HPI natural molecules as well as its analogues for the interests of medicinal chemistry.

A major focus of our research group is the use of metal mediated sequential reactions to assemble the key structure units of the target molecules [60–63]. Our synthesis of the HPI alkaloids initiated in the early 2008. We successfully developed a sequential reaction for the synthesis of mesembrine [60] and esermethole [61] using palladium chemistry. In 2012, we developed a copper catalyzed arylation of o-bromoanilides assisted by a remote sulfynilamide or carbamate auxiliary [62]. Very recently, we established a novel copper catalyzed asymmetric arylation-oxidative dimerization of o-haloanilide derivatives (Scheme 1) to construct the vicinal C3α–C3α′ all carbon quaternary stereocenters required for the synthesis of dimeric HPI compounds [64]. In this paper, we report our full accounts of new strategy towards the synthesis of (+)-chimonanthine, (+)-folicanthine, (−)-calycanthine, (−)-ditryptophenaline and its analogues.

2 Results and Discussion

The syntheses of dimeric HPI alkaloids began in the early 1960, and after endeavours of many research groups, the bio-inspired oxidative dimerization reaction of tryptamine and tryptophan derivatives has been developed to be a powerful method for the construction of dimeric HPI alkaloids [38–58, 64]. In comparison with oxidative dimerization of tryptamine and tryptophan derivatives, however, few oxidative dimersizations of oxindole derivatives have been reported [65–74]. To the best of our knowledge, only five papers reported direct oxidative dimerization of oxindoles derivatives. Except for the method established by Rodrigo which provided the dimeric intermediate in 61 % overall yield and good diastereoselectivity (dl:meso isomers = 53:8, Scheme 2) [67], other methods unfortunately suffered from low yields [65] or

Scheme 1 Sequential process for natural product synthesis
poor diastereoselectivity [66, 68, 69]. Before we conducted this research, no asymmetric oxidative dimerization of oxindoles had been developed to form the vicinal C3–C3′ all-carbon quaternary centers.

Recently, we disclosed an asymmetric synthesis of debromoflustramine and its analogues through a copper mediated arylation followed by oxindole-alkylation [62]. We envisioned that this copper catalysed cyclization process (Scheme 1) might be applied to the synthesis of dimeric HPI alkaloids indicated in Fig. 1. A retrosynthetic analysis is outlined in Scheme 3. Key to our new strategy is to develop a sequential reaction that combines metal catalysed arylation with an in situ oxidative dimerization of the resulting oxindole intermediates (Scheme 3, converting 12 to 13). Based on this new sequential process, we would be able to synthesize the dimeric HPI alkaloids starting from o-haloanilide 12. The amides (12) bearing a chiral sulfinyl amide unit [(S) or (R)-tert-butanesulfinamide] could be synthesized according to our previous procedure. We were curious to know whether the key intermediates (13, Scheme 3), containing the vicinal C3–C3′ all-carbon quaternary centers required for dimeric HPI alkaloids, could be formed diastereoselectively in a one-pot manner by a copper catalyzed arylation of o-haloanilide (12) followed by an oxidative dimerization of the newly generated oxindole intermediates in the presence of a suitable oxidant.

Our synthesis started from commercially available o-bromoaniline and γ-butyrolactone, and (S)-(−)-tert-butanesulfanamide was used to introduce the nitrogen atom and also served as a chiral auxiliary. Amide 12a was synthesized in 68 % overall yield in six steps according to our previous procedure [62] (Scheme 4). Amide 12b was also prepared from 17a in a 97 % yield. With amides (12a and 12b) in hand, we next began to explore the key copper mediated sequential arylation-dimerization of o-bromoanilides, in the hope that the oxidative dimerization might also be effected by copper salts in an efficient and economic “one pot” operation.

The initial experiment was conducted with amide 12b under our previous optimized reaction condition [62], namely LiN(SiMe3)2 and CuI in THF at reflux (Table 1, entry 1). This condition unfortunately gave a complex mixture, with the isolated product being N-benzyl-o-bromoaniline (18, 16 % yield). After several unsuccessful experiments, we finally found that the desired sequential reaction could be realized smoothly in toluene (Table 1, entry 6). Arylation of sulfanamide 12b with catalytic amount of cuprous iodide (10 % eq.) and lithium bis(trimethylsilyl)amide (2.0 eq.) in toluene, followed by oxidation with anhydrous tert-butylhydroperoxide resulted
in dimeric diastereomers (13a + 13b, as a 5:1 mixture of diastereoisomers in 78 % yield, and 13c: the meso isomer in 7 % yield). We also isolated small amount of the C3-hydroxy-oxindole (19). Although a number of oxidants could be used to generate the desired dimeric product (13a + 13b), anhydrous tert-butyl hydroperoxide proved to be the best additive for this sequential arylation–oxidative dimerization. Next we carried out the sequential procedure with amide 12a under the optimized reaction condition. The dimeric diastereomers (13d + 13e, as a mixture of diastereoisomers) were obtained in 71 % yield, we also isolated the meso isomer 13f in 8 % yield (Table 1, entry 10).

In order to know whether the oxidative dimerization was promoted solely by tert-butyl hydroperoxide, we conducted an arylation with tris(dibenzylideneacetone)dipalladium [Pd2(dba)3] followed by oxidation with t-BuOOH. It was noteworthy that only C3-hydroxy-2-oxindole product (19, Table 1, entry 11, as a mixture of diastereoisomers at C3 position, Scheme 5) was obtained. We next carried out arylation with Pd2(dba)3 without addition of t-BuOOH and successfully obtained oxindole 19a in 61 % yield. The oxindole (19a) was then subjected to oxidation in the presence of LiN(SiMe3)2 and t-BuOOH (see Scheme 5) and provided C3-hydroxy-2-oxindole (19) as the sole product.

The fact that no dimerization products (13a, 13b or 13c) formed in the absence of a copper salt suggests that the copper(II) ion, rather than tert-butyl hydroperoxide, plays the role of oxidizing the carbanion to a radical in the dimerization process. Tert-butyl hydroperoxide just serves as an oxidant to convert copper(I) to copper(II) in the oxidative dimerization process.

### Table 1  Attempted conditions for copper catalyzed sequential arylation-oxidative dimerization of o-bromoanilide 12a and 12b

| Entries | Metal salts, solvents | Oxidants | Products: yields (%) |
|---------|-----------------------|----------|----------------------|
| 1       | Cul, THF              | AIR      | 18: 16; Complex mixture<sup>a</sup> |
| 2       | Cul, toluene          | AIR      | 19: 62; 13a + b: 18; 13c: 7<sup>a</sup> |
| 3       | Cul, toluene          | I<sub>2</sub> | 19: 5; 13a + b: 53; 13c: 8<sup>a</sup> |
| 4       | Cul, toluene          | Cl<sub>2</sub> | 19: 6; 13a + b: 43; 13c: 9<sup>a</sup> |
| 5       | Cul, toluene          | Mn(OAc)<sub>3</sub>–2H<sub>2</sub>O | 19: 4; 13a + b: 53; 13c: 10<sup>a</sup> |
| 6       | Cul, toluene          | t-BuOOH  | 19: 2; 13a + b: 78; 13c: 7<sup>a</sup> |
| 7       | Cul, benzene          | t-BuOOH  | 19: 2; 13a + b: 62; 13c: 9<sup>a</sup> |
| 8       | Cul, mesitylene       | t-BuOOH  | 19: 2; 13a + b: 68; 13c: 8<sup>a</sup> |
| 9       | CuOAc, toluene        | t-BuOOH  | 19: 7; 13a + b: 58; 13c: 10<sup>a</sup> |
| 10      | Cul, toluene          | t-BuOOH  | 13d + e: 71; 13f: 8<sup>a</sup> |
| 11      | Pd<sub>2</sub>(dba)<sub>3</sub>, toluene | t-BuOOH | 19: 51; 13a + b and 13c: none<sup>b</sup> |

Yields represent isolated yields, average of two runs. All arylation reactions were conducted at 2 mmol scale under argon for 5–6 h, then addition of oxidants (2.2 mmol) or open to air

<sup>a</sup> Copper salts (0.1 eq.), LiN(SiMe<sub>3</sub>)<sub>2</sub> (2.0 eq.), designated solvent, 80 °C

<sup>b</sup> Pd<sub>2</sub>(dba)<sub>3</sub> (0.05 eq.), Ph<sub>3</sub>P (0.2 eq.), LiN(SiMe<sub>3</sub>)<sub>2</sub> (2.0 eq.), toluene, 80 °C

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![Scheme 5 Palladium catalyzed arylation of o-bromoanilide 12b](image-url)
Next, we came to the issue of determining diastereoselectivity induced by remote tert-butanesulfinamide moiety. Although the major product (13a and 13b) of this reaction was an unseparable mixture of diastereoisomers (C3S–C3S and C3R–C3R) by silica gel column chromatography, the ratio could be readily determined by proton nuclear magnetic resonance (1H-NMR; 84:16, see Electronic supplementary material). The enantioselectivity for the formation of vicinal C3–C3 quaternary carbon center was also determined after oxidation of the tert-butylsulfinyl group with 3-chloroperbenzoic acid (m-CPBA) in dichloromethane. A 66% enantioselective excess was recorded (see Electronic supplementary material for chiral HPLC analysis) under our optimum reaction condition (Table 1, entry 6). The enantioselectivity for compounds 13d and 13e was also determined after oxidation of the tert-butylsulfinyl group with 3-chloroperbenzoic acid (m-CPBA) and relatively low enantioselective excess (35%) was observed. To the best of our knowledge, this is the first example of copper catalyzed sequential arylation–dimerization of an o-bromoanilide, a high-yield procedure and also the first asymmetric oxidativeimerization of an oxindole derivative with good diastereoselectivity (dr = 10:1) and enantioselectivity (ee = 66%). The absolute stereochemistry was late confirmed by the total synthesis of (+)-chimonanthine (Scheme 10). A working hypothesis was proposed for prediction of C3–C3 configuration in Scheme 6, p–p Stack (for a review for p–p.stack in asymmetric synthesis, see: [75, 76]) might play important role for the enantioselectivity as well as diastereoselectivity.

In order to access the starting material for the synthesis of ditryptophenaline, we started the synthesis of amide 12c (Scheme 7). Nucleophilic addition of vinyl magnesium bromide to aldimine 17a unfortunately provided two isolatable diastereoisomers (20a and 20b) in a ratio of 3.4–1 (see Scheme 7). This problem was soon fixed by addition of Grignard reagent to aldimine 17c, a surrogate prepared from o-idoaniline. Better diastereoselectivity (dr = 10:1, see Scheme 7) was obtained by 1,2-addition of vinyl magnesium bromide to o-idoanilide 17c. After benzylation, we obtained 12c in 58% yield in six steps from iodoaniline. The absolute configuration for the newly generated chiral center of compound 12c was deduced by Cram’s chelation model [77] and late confirmed by X-ray crystallography (Schemes 8, 9) and our total synthesis of (−)-ditryptophenaline (Scheme 11).

We next conducted the arylation–oxidative dimerization reaction with substrate 12c under the optimized condition. This reaction afforded the dimerization products in good yield, and all dimeric diastereomers were isolated by silica gel column chromatography, with the desired isomer (21a) being obtained as the major product and in a 50% yield (Scheme 8). It was noteworthy that this sequential arylation–oxidative dimerization process could be conducted on multi-gram scale in the presence of only catalytic amount of cuprous iodide (10%). In order to determine the absolute configuration of compound 21a, we converted it to sulfonyl ester 23 and successfully obtained a suitable crystal for X-ray crystallography. The absolute configuration was confirmed by X-ray crystallography with Mo Kα radiation (Scheme 9).

Having successfully established the cascade process, we next initiated the synthesis of (+)-chimonanthine and its related natural dimeric HPI alkaloids. Based on our working hypothesis (Scheme 6), we used (R)-(+)–tert-butanesulfonamide as a chiral auxiliary. Treatment of 11a
with (R)-(+) -tert -butanesulfinamide in the presence of
titanium ethoxide [Ti(OEt) 4] in THF afforded 17a in 94 %
yield. After reduction and benzylation, amide 12b was
synthesized in 68 % overall yield from o-bromoaniline.
The key arylation–oxidative dimerization of 12b (at multi-
gram scale, 5.42 g, 10 mmol, see Scheme 10) afforded 13a’ + 13b’ in 78 % yield. Treatment of this diastere-
omeric mixture with 4 N HCl in methanol gave diamine 24
in a 95 % yield. After recrystallization in methanol with 2 N aqueous solution of HCl (2.0 eq.), the isomeric purity
of di-amine 24 was greater than 99 %, as determined by
HPLC analysis (Scheme 10, see supporting information).
The reductive amination of 24 with formaldehyde and
NaBH(OAc) 3 provided diamide 25 (96 %) [19, 28].
Selective debenzylation of the amine benzyl group in 25 by
reaction with α-chloroethyl chloroformate (ACE-Cl) [77]
followed by reflux in methanol afforded diamine 26 (95 %). Reductive aminocyclization of diamine 26 in THF
in the presence of diisobutylaluminum hydride (DIBAL-H)
provided desired HPI precursor (27) in 54 % yield. Finally,
removal of the benzyl protecting groups by a Birch
reduction [19] afforded (+)-chimonanthine in 95 % yield
([α] D = +285, c 0.12, EtOH, lit. [71], [α] D = +279, c 0.1,
EtOH, lit. [28], [α] D = +254, c 1.0, EtOH). The NMR
spectra of our synthetic sample were in full agreement
with those reported in the literature [19, 20, 28].
Treatment of chimonanthine with formaldehyde in the
presence of sodium triacetoxyborohydride [28] then fur-
nished (+)-folicanthine (95 %, [α] D = +315, c 0.10,
MeOH, lit. [70], [α] D = +318, c 0.11, MeOH, lit. [71],
[α] D = +314, c 0.25, MeOH). Upon exposure of chimo-
nanthine to acid at reflux for 8 h [19, 28] (−)-calycanthine
([α] D = −615, c 0.15, EtOH, lit. [28], [α] D = −612,
c 0.18, EtOH) was obtained in 52 % isolated yield
(Scheme 10).
Starting from intermediate 21a, synthesis of (−)-ditryptophenaline was also investigated (Scheme 11). Removal of the tert-butanesulfinyl group by treatment of 21a with 4 N HCl in methanol afforded diamine 28. Selectively deprotection of the benzyl groups attaching to amines was difficult due to the presence of double bonds but finally achieved after many experiments. Treatment of diamine 28 with N-chlorosuccinimide, followed by deprotonation with t-BuOK provided imine [79], which, upon exposure to phenylhydrazine in ethanol [80], gave the primary diamine 29 in 84 % overall yield. After reductive aminocyclization with DABAL-H and debenzylation with metal lithium in liquid ammonia (Scheme 11), intermediate 31 was obtained in 49 % yield over two steps. Condensation of intermediate 31 with Fmoc-methylphenaline afforded compound 32 (FMOC-(S)-MePhe–OH, HATU and Et₃N in DMF) in 87 % yield [33]. Cleavage of the double bond led to aldehyde 33, and oxidation with buffered NaClO₂ provided diacid 34 [21]. Finally the diacid 34 was converted to (−)-ditryptophenaline ( [α]D = −292, c 0.40, CH₂Cl₂, lit. [29], [α]D = −292, c 0.97, CH₂Cl₂, lit. [49], [α]D = −291, c 0.41, CH₂Cl₂) in 83 % overall yield by following Overman’s procedure, deprotection with piperidine in THF and cyclization with DCC in dichloromethane (Scheme 11) [21]. The NMR spectra of our synthetic sample were in complete agreement with the reported data.

In conclusion, we have developed the first copper catalyzed arylation–oxidative dimerization of o-haloanilides with a remote assistance of an intramolecular sulfinyl amide unit. Based on this method, a general synthetic
strategy has been successfully established for the total synthesis of chimonanthine, folicanthine, calycanthine and ditryptophenaline. This copper catalyzed sequential arylation–oxidative dimerization should find further application in the synthesis of HPI alkaloids as well as its medicinally interesting analogues.

3 Experimental Section

3.1 General Experimental

$^1$H-NMR spectra were recorded on a Bruker Avance 300 or 400 spectrometer at 300 or 400 MHz. Carbon-13 nuclear magnetic resonance ($^{13}$C-NMR) was recorded on Bruker Avance 300 or 400 spectrometer at 75 or 100 MHz. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane for all recorded NMR spectra. Low-resolution mass spectra were recorded on a VG Auto Spec-3000 magnetic sector MS spectrometer. High resolution mass spectra were taken on AB QSTAR Pulsar mass spectrometer or Agilent G6230 TOF MS spectrometer. Chiral HPLC analyses were performed on Agilent 1100 series with a tunable UV detector at wavelength $\lambda = 254$ nm. Melting points were determined on a capillary melting point apparatus and are uncorrected. Optical rotations were obtained on a UV-210A spectrometer. Starting materials and reagents used in reactions were obtained commercially from Acros, Aldrich, J&K and were used without purification, unless otherwise indicated. THF and toluene used in the reactions were dried by distillation over metallic sodium; dichloromethane were distilled over P$_2$O$_5$. Unless otherwise stated, all reactions were conducted in dried glassware under a positive pressure of dry nitrogen or argon. Silica gel (Qingdao, 200–300 mesh) was used for column chromatography.

3.2 Synthesis of Compound 15a

2-Bromoaniline (12.04 g, 70.0 mmol) was dissolved in toluene (200 mL) under nitrogen. To this mixture, a solution of trimethylaluminum in toluene (2.0 M, 49 mL, 98.0 mmol, 1.4 eq.) was added dropwise at 0 °C. The resulting mixture was then stirred at room temperature for 45 min. $\gamma$-Butyrolactone (7.5 mL, 98 mmol, 1.4 eq.) was added via syringe and the reaction mixture was stirred at room temperature overnight. The solidified mixture was then stirred at room temperature for 8 h. After filtration through a short column of silica gel and washed with ethyl acetate (180 mL), the combined organic phases were washed with brine (50 mL) and dried over anhydrous sodium sulfate. After removal of the solvent, the crude products were chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 1:2) to provide amide 15a (17.34 g, 96 %) as a white solid.

m.p. 65–67 °C. $R_t$ 0.55 (petroleum ether:ethyl acetate = 1:2). $^1$H-NMR (300 MHz, CDCl$_3$), δ (ppm) 8.27 (1H, $d$, $J = 7.8$ Hz), 7.81 (1H, $b_r$s), 7.53 (1H, $d$, $J = 7.8$ Hz), 7.30 (1H, $t$, $J = 7.8$ Hz), 6.98 (1H, $t$, $J = 7.8$ Hz), 3.75 (2H, $m$), 2.59 (3H, $t$, $J = 6.9$ Hz), 2.05–1.91 (2H, $m$). $^{13}$C-NMR (75 MHz, CDCl$_3$) δ (ppm) 171.73, 135.72, 132.41, 128.48, 125.48, 122.42, 113.71, 62.06, 34.80, 28.04. +TOF-MS m/z (%) 282 (M$^+$+1+Na, 100 %), 281 (M$^+$+Na, 8 %), 280 (M$^+$+Na, 96 %), 260 (42), 258 (40), 240 (20), 200 (9), 174 (29), 172 (30), HRMS m/z Found 258.0124, Calcd. for C$_{10}$H$_{13}$NO$_2$NaBr [M+1]$^+$ 258.0129.

3.3 Synthesis of Compound 16a

To a mixture of cesium carbonate (17.43 g, 53.5 mmol, 1.5 eq.) in acetonitrile (90 mL) and N,N-dimethylformamide (DMF, 45 mL) at 0 °C was added dropwise a solution of amide 15a (9.20 g, 35.7 mmol) in acetonitrile (10 mL) and DMF (5 mL). Benzyl bromide (6.4 mL, 53.5 mmol, 1.5 eq.) was then added. The resulting mixture was allowed to stir at room temperature for 8 h. After filtration through a short column of silica gel and washed with ethyl acetate (180 mL), the combined organic phases were concentrated under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 1:1) to afford alcohol 16a (11.86 g, 96 %) as a colorless oil.

$R_t$ 0.60 (petroleum ether:ethyl acetate = 1:1). $^1$H-NMR (KBr, thin film) cm$^{-1}$ 3417, 2963, 1651, 1402, 1270, 1203, 1050, 728. $^1$H-NMR (300 MHz, CDCl$_3$), δ (ppm) 7.68 (1H, $dd$, $J = 2.7$, 7.8 Hz), 7.37–7.12 (7H, $m$), 6.77 (1H, $dd$, $J = 3.3$, 7.8 Hz), 5.64 (1H, $d$, $J = 14.4$ Hz), 4.01 (1H, $d$, $J = 14.4$ Hz), 3.71–3.55 (2H, $m$), 2.89–2.68 (1H, $m$), 2.14 (2H, $t$, $J = 6.6$ Hz), 1.98–1.78 (2H, $m$). $^{13}$C-NMR (75 MHz, CDCl$_3$) δ (ppm) 173.43, 140.71, 136.99, 134.07, 131.52, 130.03, 129.46, 128.55, 127.72, 123.86, 62.78, 51.77, 32.06, 27.85. +TOF-MS m/z (%) 372 (M$^+$+1+Na, 99 %), 371 (M$^+$+Na, 9 %), 370 (M$^+$+Na, 100 %), 350 (32), 348 (34), 330 (2), 264 (3). HRMS m/z Found 370.0410, Calcd. for C$_{17}$H$_{18}$NO$_2$NaBr [M+23]$^+$ 370.0418.

3.4 Synthesis of Compound 11a

Alcohol 16a (11.86 g, 34.1 mmol) was dissolved in dichloromethane (120 mL). To this solution, a powder of Dess–Martin periodinane (21.67 g, 51.1 mmol, 1.5 eq.) was added. The resulting mixture was then stirred at room temperature for 6 h. After filtration through a short column of silica gel and washed with ethyl acetate (150 mL), the
combined organic phases were concentrated under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 3:1) to afford aldehyde 11a (10.85 g, 92 %) as white plates. m.p. 52–54 °C. Rf 0.53 (petroleum ether:ethyl acetate = 3:1). FTIR (KBr, thin film) cm⁻¹ 3419, 3060, 2921, 2827, 2730, 1657, 1400, 1265, 1196, 1020, 79 3.5 Synthesis of Compound 17b
To a solution of aldehyde 11a (5.85 g, 16.8 mmol) in toluene (60 mL) was added a powder of (S)-(−)-tert-butanesulfonamide (4.1 g, 33.7 mmol, 2.0 eq.) and KHSO₄ (4.56 g, 33.7 mmol, 2.0 eq.). The resulting mixture was stirred at 45 °C for 3 h. After filtration through a short column of silica gel and washed with ethyl acetate (80 mL), the combined organic phases were concentrated under reduced pressure and the residue was flash chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 3:1) to afford the sulfinyl imine (17a: 7.36 g, 97 %) as colorless syrup. The sulfinyl imine was re-dissolved in anhydrous methanol (60 mL) and the resulting solution was cooled to 0 °C. A powder of sodium borohydride (1.87 g, 49.2 mmol, 3.0 eq.) was added in small portion over a period of 30 min. The resulting mixture was then allowed to stir at 0 °C for 4 h. After which, a saturated solution of NH₄Cl (20 mL) was introduced and the resulting mixture was concentrated (ca. 20–30 mL). The mixture was diluted with water (100 mL) and extracted with ethyl acetate (4 × 50 mL). The combined organic phases were washed with brine (60 mL) and dried over anhydrous sodium sulfate. After removal of the solvent, the crude products were chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 1:2) to provide sulfinamide 17b (6.6 g, 89 %) as a white solid. m.p. 102–103 °C. [α]D²⁰ +71 (c 0.90, CHCl₃). Rf 0.45 (petroleum ether:ethyl acetate = 1:2). FTIR (KBr, thin film) cm⁻¹ 3244, 3063, 2950, 2868, 1662, 1559, 1468, 1398, 1266, 1203, 1063, 947, 767, 732, 628. ¹H-NMR (as a mixture of rotamers, 300 MHz, CDCl₃), δ (ppm) 7.71–7.61 (1H, m), 7.31–7.12 (7H, m), 6.81–6.70 (1H, m), 5.58 (1H, d, J = 14.1 Hz), 4.00 (0.5H, d, J = 14.1 Hz) [3.99 (0.5H, d, J = 14.1 Hz)], 3.42–3.23 (1H, m), 3.22–3.10 (1H, m), 3.10–2.94 (1H, m), 2.11–1.97 (2H, m), 1.93–1.78 (2H, m), 1.13 (9H, s). ¹³C-NMR (rotamer in brackets, 75 MHz, CDCl₃), δ (ppm) 172.16, 140.67, 137.02, 134.00 (133.94), 131.57 (131.50), 129.54, 128.47, 127.63, 123.85, 55.64, 51.58, 45.07 (44.99), 31.62, 26.15, 22.71. +TOF-MS m/z (%) 475 (M⁺+1+Na, 60 %), 474 (M⁺+Na, 8 %), 473 (M⁺+Na, 65 %), 453 (98), 452 (12), 451 (100), 435 (25), 433 (23), 402 (4), 400 (4), 294 (2), 282 (6), 280 (5), 262 (2). HRMS m/z Found 473.0873. Calcd. for C₂₁H₂₇N₂O₂NaSBr [M+Na]+ 473.0874. 3.6 Synthesis of Compound 12a
To a mixture of sodium hydride (60 % in mineral oil, 1.22 g, 30.5 mmol, freshly washed with anhydrous hexane three times under nitrogen) in anhydrous THF (50 mL) at 0 °C was added a solution of sulfonamide 17b (10.6 g, 23.5 mmol) in THF (50 mL) via syringe. After stirring at 0 °C for 30 min, methyl iodide (1.9 mL, 30.6 mmol) was added. The resulting mixture was then stirred at room temperature for 15 h under nitrogen. A powder of NH₄Cl (1.62 g, 30.0 mmol) was added and the mixture was stirred for 10 min. After concentrated under reduced pressure, the residue was diluted with water (100 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine (20 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 1:1) to afford the product (12a: 10.03 g, 92 %) as a white solid. m.p. 60–62 °C. Rf 0.52 (petroleum ether:ethyl acetate = 1:1). ¹H-NMR (300 MHz, CDCl₃), δ (ppm) 7.65–7.58 (1H, m), 7.28–7.08 (7H, m), 6.78–6.68 (1H, m), 5.57 (1H, d, J = 2.1, 14.4 Hz), 3.95 (1H, d, J = 14.4 Hz), 3.01–2.82 (2H, m), 2.52 (3H, s), 2.01–1.78 (4H, m), 1.09 (9H, s). ¹³C-NMR (75 MHz, CDCl₃), δ (ppm) 171.77, 140.51, 136.93, 133.86, 131.42, 129.86, 129.24, 128.43, 128.36, 127.51, 127.36, 58.11, 53.94 (53.57), 51.41, 32.65 (32.48), 23.64, 23.43. +TOF-MS m/z (%) 489 (M⁺+1+Na, 100 %), 488 (M⁺+Na, 12 %), 487 (M⁺+Na, 98 %), 467 (18), 465 (16), 432 (2), 383 (1), 375 (2), 361 (21), 359 (20), 276 (3), 274 (2). HRMS m/z Found 487.1023. Calcd. for C₁₂H₁₁N₂Na₂Br [M+Na]+ 487.1030. 3.7 Synthesis of Compound 12b
To a mixture of sodium hydride (60 % in mineral oil, 1.32 g, 33 mmol, 1.5 eq., freshly washed with anhydrous...
hexane three times under nitrogen) in anhydrous THF (30 mL) at 0 °C was added a solution of sulfonamide 17b (9.9 g, 22 mmol) in THF (80 mL) via syringe. After stirring at 0 °C for 30 min, benzyl bromide (3.9 mL, 33 mmol, 1.5 eq.) was added. The resulting mixture was then stirred at 0 °C for 2 h, then at room temperature for 12 h under nitrogen. A powder of NH₄Cl (1.62 g, 30.0 mmol) was added and the mixture was stirred for 10 min. After concentration under reduced pressure, the residue was diluted with water (60 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine (30 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 2:1) to afford the product (12b: 11.2 g, 94 %) as an off-yellow oil.

\[ \text{[2]20}^\circ = 3.9 \text{ (c 0.40, CHCl₃), } R_f 0.51 \text{(petroleum ether:ethyl acetate = 2:1). } \]

To a mixture of amide 15b (29.3 g, 96 mmol), cesium carbonate (46.9 g, 144 mmol, 1.5 eq.) in acetonitrile (200 mL) and N,N-dimethylformamide (DMF, 100 mL) at 0 °C was added dropwise a solution of benzyl bromide (17.1 mL, 144 mmol, 1.5 eq.) was then added. The resulting mixture was then stirred at room temperature for 12 h. After filtration through a short column of silica gel and washed with ethyl acetate (200 mL), the combined organic phases were concentrated under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 1:1) to afford alcohol 16b (36.03 g, 95 %) as a white powder.

\[ \text{[3]20}^\circ = 72–74 \text{ °C, } R_f 0.55 \text{(petroleum ether:ethyl acetate = 1:1). } \]

3.8 Synthesis of Compound 15b

2-Iodoaniline (21.9 g, 100.0 mmol) was dissolved in toluene (300 mL) under nitrogen. To this mixture, a solution of trimethylaluminum in toluene (2.0 M, 60 mL, 120 mmol, 1.2 eq.) was added dropwise at 0 °C. The resulting mixture was then stirred at room temperature for 45 min, after which, \( \gamma \)-butyrolactone (9.2 mL, 120 mmol, 1.2 eq.) was added via syringe and the reaction mixture was stirred at room temperature overnight. The solidified mixture was then cooled to 0 °C and HCl (1 N, 360 mL) was added slowly. After 1 h, the resulting mixture was extracted with ethyl acetate (4 × 150 mL). The combined organic phases were washed with brine (100 mL) and dried over anhydrous sodium sulfate. After removal of the solvent, the crude products were chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 1:2) to provide amide 15b (29.30 g, 96 %) as a white solid.

m.p. 65–66 °C, \( R_f \) 0.59 (petroleum ether:ethyl acetate = 1:2). \( ^{1}H-NMR \) (KBr, thin film) cm⁻¹ 3268, 2935, 1658, 1528, 1430, 1287, 1059, 749, 664. \( ^{13}C-NMR \) (400 MHz, CDCl₃), \( \delta \) (ppm) 8.02 (1H, \( d, J = 8.0 \text{ Hz} \)), 7.76 (1H, s), 7.75 (1H, \( d, J = 8.0 \text{ Hz} \)), 7.30 (1H, \( t, J = 7.6 \text{ Hz} \)), 6.83 (1H, \( t, J = 7.6 \text{ Hz} \)), 3.72 (2H, \( t, J = 6.0 \text{ Hz} \)), 3.32 (1H, brs), 2.56 (3H, \( t, J = 6.9 \text{ Hz} \)), 2.05–1.91 (2H, \( m \)). \( ^{1}H-NMR \) (100 MHz, CDCl₃) \( \delta \) (ppm) 171.92, 138.90, 138.16, 129.16, 126.43, 123.11, 91.14, 61.76, 34.52, 28.06. EI–MS \( m/z \) (%): 304 (M⁺, 28 %), 268 (89 %), 224 (12 %), 182 (30), 180 (40), 152 (10), 128 (6), 104 (12), 91 (100). \( HRMS \) \( m/z \) Found 304.9969, Calcd. for C₁₀H₁₂NO₂I [M⁺] 304.9913.

3.9 Synthesis of Compound 16b

To a mixture of amide 15b (29.3 g, 96 mmol), cesium carbonate (46.9 g, 144 mmol, 1.5 eq.) in acetonitrile (200 mL) and N,N-dimethylformamide (DMF, 100 mL) at 0 °C was added dropwise a solution of benzyl bromide (17.1 mL, 144 mmol, 1.5 eq.) was then added. The resulting mixture was then stirred at room temperature for 12 h. After filtration through a short column of silica gel and washed with ethyl acetate (200 mL), the combined organic phases were concentrated under reduced pressure and the residue was chromatographed on silica gel (petroleum ether 60–90 °C;ethyl acetate = 1:1) to afford alcohol 16b (36.03 g, 95 %) as a white powder.

m.p. 72–74 °C, \( R_f \) 0.55 (petroleum ether:ethyl acetate 1:1). \( ^{1}H-NMR \) (KBr, thin film) cm⁻¹ 3500, 2940, 2871, 1631, 1405, 1322, 1051, 1008, 731, 616, 491. \( ^{13}C-NMR \) (400 MHz, CDCl₃), \( \delta \) (ppm) 7.95 (1H, \( dd, J = 1.2, 8.0 \text{ Hz} \)), 7.28–7.15 (6H, \( m \)), 7.03 (1H, \( ddd, J = 1.2, 7.8 \text{ Hz} \)), 6.71 (1H, \( dd, J = 1.2, 7.8 \text{ Hz} \)), 5.67 (1H, \( d, J = 14.4 \text{ Hz} \)), 3.91 (1H, \( d, J = 14.4 \text{ Hz} \)), 3.70–3.53 (2H, \( m \)), 3.12–3.04 (1H, \( m \)), 2.10 (2H, \( t, J = 6.6 \text{ Hz} \)), 1.92–1.78 (2H, \( m \)). \( ^{13}C-NMR \) (100 MHz, CDCl₃) \( \delta \) (ppm) 173.18, 143.80, 140.31, 136.83, 130.83, 130.00, 129.43, 129.35, 128.47, 127.65, 100.36, 62.51, 51.81, 32.23, 27.79. EI–MS \( m/z \) (%): 395 (M⁺, 10 %), 351 (3 %), 309 (20 %), 224 (4 %), 203 (5), 182 (15), 180 (30), 152 (6), 134 (9), 119 (17), 104 (7), 91 (100), 77 (14). \( HRMS \) \( m/z \) Found 395.0378, Calcd. for C₁₇H₁₈NO₂I [M⁺] 395.0382.

3.10 Synthesis of Compound 11b

Alcohol 16b (36.0 g, 91.1 mmol) was dissolved in dichloromethane (300 mL). To this solution, a powder of Dess-Martin periodinane (46.4 g, 109.3 mmol, 1.2 eq.) was added. The resulting mixture was then stirred at room.
temperature for 3 h. After filtration through a short column of silica gel and washed with ethyl acetate (150 mL), the combined organic phases were concentrated and the residue was chromatographed on silica gel (petroleum ether 60–90 °C; ethyl acetate = 3:1) to afford aldehyde 11b (32.94 g, 92 %) as pale yellow plates.

m.p. 76–78 °C. Rf 0.53 (petroleum ether:ethyl acetate = 3:1). FTIR (KBr, thin film) cm⁻¹: 3433, 3056, 2826, 1713, 1651, 1400, 1268, 1017, 771, 724. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) 9.77 (1H, s), 7.93 (1H, dd, J = 1.2, 8.0 Hz), 7.29–7.13 (6H, m), 7.01 (1H, dd, J = 1.2, 7.8, 8.0 Hz), 6.83 (1H, dd, J = 1.2, 7.8 Hz), 5.65 (1H, d, J = 14.4 Hz), 3.92 (1H, d, J = 14.4 Hz), 2.86 (1H, ddd, J = 6.0, 7.6, 18.7 Hz), 2.65 (1H, dt, J = 6.0, 18.7 Hz), 2.32 (1H, ddd, J = 6.0, 7.6, 17.1 Hz), 2.18 (1H, dt, J = 6.0, 17.1 Hz). ¹³C-NMR (100 MHz, CDCl₃), δ (ppm) 200.64, 170.60, 143.34, 139.98, 136.49, 130.65, 129.86, 129.21, 128.99, 128.18, 127.33, 100.11, 51.54, 38.57, 27.26. EI–MS m/z (%) 393 (M⁺, 12 %), 369 (3 %), 351 (3 %), 309 (28), 282 (5), 268 (70), 230 (4), 224 (4), 203 (9), 182 (23), 180 (63), 152 (12), 104 (7), 91 (100), 77 (13). HRMS m/z: Found 393.0265, Calcd. for C₁₇H₁₆NO₂I [M⁺] 393.0226.

3.11 Synthesis of Compound 17c

To a solution of aldehyde 11b (19.7 g, 50 mmol) in THF (200 mL) was added a powder of (S)-(−)-tert-butanesulfonamide (12.1 g, 100 mmol, 2.0 eq.) and Ti(OEt)₄ (22.8 g, (200 mL) was added a powder of (S)-((1H, 78 %) as pale yellow plates.

A solution of imine 17c (19.8 g, 40 mmol) in dichloromethane (200 mL) was stirred at −78 °C for 10 min. To this mixture was added slowly a solution of vinyl magnesium bromide in THF (1.0 M, 60 mL, 60 mmol, 1.5 eq.). The reaction mixture was then stirred at −78 °C for 5 h before warming up to room temperature. Saturated NH₄Cl aqueous solution (80 mL) was introduced and the resulting mixture was stirred at room temperature for 1 h. The mixture was diluted with water (150 mL) and extracted with dichloromethane (3 × 100 mL) and the combined organic phases were dried over anhydrous Na₂SO₄. After filtration and concentrated, the residue was chromatographed on silica gel (petroleum ether 60–90 °C; ethyl acetate = 2:1) to afford the major amide (20c: 16.35 g, 78 %) as a yellow syrup. Further elution with solvents (petroleum ether 60–90 °C; ethyl acetate = 1:2) provided the minor sulfamidine 20d (1.64 g, 7.8 %) as a pale yellow oil.

3.12 Synthesis of Compound 20c

A solution of imine 17c (19.8 g, 40 mmol) in dichloromethane (200 mL) was stirred at −78 °C for 10 min. To this mixture was added slowly a solution of vinyl magnesium bromide in THF (1.0 M, 60 mL, 60 mmol, 1.5 eq.). The reaction mixture was then stirred at −78 °C for 5 h before warming up to room temperature. Saturated NH₄Cl aqueous solution (80 mL) was introduced and the resulting mixture was stirred at room temperature for 1 h. The mixture was diluted with water (150 mL) and extracted with dichloromethane (3 × 100 mL) and the combined organic phases were dried over anhydrous Na₂SO₄. After filtration and concentrated, the residue was chromatographed on silica gel (petroleum ether 60–90 °C; ethyl acetate = 2:1) to afford the major amide (20c: 16.35 g, 78 %) as a yellow syrup. Further elution with solvents (petroleum ether 60–90 °C; ethyl acetate = 1:2) provided the minor sulfamidine 20d (1.64 g, 7.8 %) as a pale yellow oil.

3.12.1 Major: 20c

[20]²⁺ +20 (c 0.50, CHCl₃). Rf 0.56 (petroleum ether:ethyl acetate = 1:1). FTIR (KBr, thin film) cm⁻¹: 3433, 3063, 2964, 1663, 1466, 1400, 1079. ¹H-NMR (as a mixture of rotamers, 400 MHz, CDCl₃), δ (ppm) 8.09 (1H, brs), 7.93 (1H, d, J = 8.0 Hz), 7.28–7.14 (6H, m), 7.08–7.01 (1H, m), 6.75 (0.5H, d, J = 7.6 Hz) [6.74 (0.5H, d, J = 7.6 Hz)], 5.67 (0.5H, d, J = 14.4 Hz) [5.59 (0.5H, d, J = 14.0 Hz)], 3.97 (0.5H, d, J = 14.0 Hz) [3.92 (0.5H, d, J = 14.4 Hz)], 3.00–2.87 (1H, m), 2.81–2.68 (1H, m), 2.46–2.18 (2H, m), 1.14 (4.5H, s) [1.12 (4.5H, s)]. ¹³C-NMR (rotamer in brackets, 100 MHz, CDCl₃), δ (ppm) 170.51 (170.39), 168.11 (168.06), 143.54, 140.20 (140.13), 136.69 (136.60), 130.76 (130.65), 129.89, 129.45 (129.24), 129.13, 128.24, 127.45 (127.42), 100.24, 56.57 (56.53), 51.71 (51.55), 31.13 (30.99), 29.88 (29.83), 22.25 (22.22). EI–MS m/z (%) 496 (M⁺, 10 %), 395 (3), 378 (16), 309 (10), 298 (15), 268 (20), 253 (4), 224 (2), 201 (7), 182 (11), 180 (20), 152 (5), 133 (21), 119 (46), 103 (6), 91 (100), 77 (14). HRMS m/z: Found 496.0663, Calcd. for C₂₁H₂₃N₂O₂SI [M⁺] 496.0682.
3.12.2 Minor: 20d

\[ \frac{[\text{z}]_{D}^{20}}{[\text{z}]_{D}^{20}} + 1 \text{ (c 0.20, CHCl}_{3}). \] \[ R_{f} 0.53 \text{ (petroleum ether:ethyl acetate = 1:1).} \] \[ ^{1}H-NMR \text{ (300 MHz, CDCl}_{3}, \delta \text{ (ppm) 7.37–7.13 (7H, m), 6.99–6.90 (2H, m), 5.76 (1H, } \text{ddd}, J = 6.0, 9.0, 18.0 \text{ Hz), 5.17 (1H, } d, J = 18.0 \text{ Hz), 5.08 (1H, } d, J = 9.0 \text{ Hz), 4.87 (2H, } s, J = 6.0, 15.0 \text{ Hz), 3.50 (1H, } d, J = 9.0 \text{ Hz), 2.20–2.05 (2H, } m, J = 16.5 \text{ Hz). EI–MS } m/z 128.91, 128.43, 128.14, 127.46, 116.62, 58.79, 56.07, 53.13, 30.92, 30.75, 22.65. \] 

Synthesis of Compound 12d

To a mixture of sodium hydride (60 % in mineral oil, 1.87 g, 46.7 mmol, 1.5 eq., freshly washed with anhydrous THF) was added benzyl bromide (5.5 mL, 10.5 mmol, 1.5 eq.) was added. The reaction mixture was stirred at 0 °C for 10 min. After concentrated under reduced pressure, the residue was chromatographed on silica gel (petroleum ether:ethyl acetate 1:1). 1H-NMR (300 MHz, CDCl}_{3}, \delta (ppm) 7.90 (1H, t, J = 7.6 Hz), 6.64 (0.5H, dd, J = 1.2, 7.6 Hz), 6.60 (0.5H, dd, J = 1.2, 7.6 Hz), 5.74–5.59 (2H, m), 5.06 (1H, dd, J = 6.8, 10.0 Hz), 4.97 (1H, t, J = 18.0 Hz), 4.41 (1H, dd, J = 10.0, 16.4 Hz), 4.02 (1H, d, J = 16.4 Hz), 3.85 (1H, t, J = 14.0 Hz), 3.59–3.38 (1H, m), 2.35–2.17 (1H, m), 2.03–1.80 (3H, m), 1.12 (9H, s). 13C-NMR (rotamer in brackets, 75 MHz, CDCl}_{3}, \delta (ppm) 172.35, 142.19, 139.47, 137.42, 129.68, 128.91, 128.43, 128.14, 127.46, 116.62, 58.79, 56.07, 53.13, 30.92, 30.75, 22.65. EI–MS m/z (%) 525 (M+1, 10 %), 511 (5), 467 (30), 404 (10), 341 (100), 309 (21), 278 (37), 250 (4), 238 (6), 225 (36), 183 (79), 180 (15), 140 (11), 112 (6), 110 (9), 91 (78), 77 (12). HRMS m/z Found 524.0996, Calcd. for C_{23}H_{29}N_{2}O_{2}SI [M]^{+} 524.0995.

3.13 Synthesis of Compound 12c

To a mixture of sodium hydride (60 % in mineral oil, 1.87 g, 46.7 mmol, 1 eq., freshly washed with anhydrous hexane three times under nitrogen) in anhydrous THF (50 mL) at 0 °C was added a solution of sulfonamide 20c (16.3 g, 31.1 mmol) in THF (150 mL) via syringe. After stirring at 0 °C for 10 min, benzyl bromide (5.5 mL, 46.7 mmol, 1.5 eq.) was added. The resulting mixture was then stirred at 0 °C for 2 h, then at room temperature for 12 h under nitrogen. A powder of NH_{4}Cl (2.7 g, 18.1 g, 95 %) as a pale yellow oil, which was characterized by 1H-NMR (31.59), 26.94 (26.88), 23.57. EI–MS m/z (%) 614 (M+, 4 %), 509 (7), 482 (3), 458 (1), 420 (4), 405 (5), 309 (5), 278 (4), 236 (2), 182 (8), 180 (13), 146 (7), 128 (5), 106 (12), 91 (100). HRMS m/z Found 614.1480, Calcd. for C_{30}H_{35}N_{2}O_{2}SI [M]^{+} 614.1464.

3.14 Synthesis of Compound 13a + 13b

A mixture of copper iodide (CuI, 133.3 mg, 0.7 mmol, 0.1 eq.) and bromoanilide 12b (3.78 g, 7.0 mmol) in anhydrous toluene (140 mL) was degassed and purged with argon (three times). A solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 14 mL, 14 mmol, 2.0 eq.) was added and the resulting mixture was stirred at 80 °C (oil bath) under argon for 5 h. After cooling to room temperature then to 0 °C, a solution of anhydrous t-BuOOH (degassed and purged with argon, ~3.0 M in toluene, 3.5 mL, 10.5 mmol, 1.5 eq.) was added. The reaction mixture was allowed to stir at 0 °C under argon for 3 h. Saturated aqueous solution of NH_{4}Cl (8 mL) was added. After 30 min, the mixture was diluted with water (100 mL). The aqueous phase was extracted with ethyl acetate (3 × 60 mL). The combined organic phases were dried over anhydrous Na_{2}SO_{4}. After removal of the solvents, the residue was chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 2:1 → 1:1 → 1:2) to afford the major product (13a + 13b, as a mixture of C_{3}–C_{3a} diastereomers, 2.51 g, 78.1 %) as pale yellow syrup. Further elution afforded the minor product (13c: meso-isomer, 0.23 g, 7.2 %) as a pale yellow oil, which was characterized after removal of the tert-butylsulfinyl group (13d). *The anhydrous tert-butylhydroperoxide (t-BuOOH) in toluene (ca. ~3.0 M) was prepared by the following procedure: 70 % aqueous solution of t-BuOOH (40.6 mL, density = 0.93 g/mL) was added to toluene (46 mL) and the resulting water (ca. 10 mL) was separated and back-extracted with toluene (2 × 10 mL). The combined organic phases were then dried over anhydrous sodium sulfate. After filtration, the resulting solution was kept with 4 Å molecular sieve and could be used for this reaction without further purification.

3.14.1 13a + 13b

An 83:17 mixture of diastereomers at C3–C3’ position: \[ R_{t} 0.45 \text{ (petroleum ether:ethyl acetate = 1:1).} \] FTIR (KBr, thin film) cm\(^{-1}\) 3396, 3057, 2957, 1705, 1609, 1460, 1360, 1176, 1072, 982, 929, 746, 703. \[ ^{1}H-NMR \text{ (400 MHz, CDCl}_{3}, \text{major C3–C3’S-isomer reported), } \delta \text{ (ppm) 7.34–7.18 (2 × 8H, m), 7.11–7.03 (2 × 2H, m), 6.81 (2 × 1H, } t, J = 7.6 \text{ Hz), 6.68 (2 × 1H, } d, J = 7.2 \text{ Hz),}\]
6.49 (2 × 1H, t, J = 7.6 Hz), 6.27 (2 × 1H, d, J = 7.6 Hz), 4.92 (2 × 1H, d, J = 15.6 Hz), 4.36 (2 × 1H, d, J = 15.6 Hz), 4.21 (2 × 2H, s), 3.10 (2 × 1H, ddd, J = 4.8, 12.4, 12.8 Hz), 2.51 (2 × 1H, ddd, J = 3.6, 12.4, 12.8 Hz), 2.37 (2 × 1H, ddd, J = 4.0, 13.2, 13.6 Hz), 2.21–2.11 (2 × 1H, m), 1.17 (2 × 9H, s). \(^{13}C\)-NMR (100 MHz, CDCl\(_3\), major C3S–C3'S-isomer reported), δ (ppm) 176.69, 142.50, 137.07, 135.38, 129.02, 128.87, 128.54, 128.39, 127.75, 127.69, 127.50, 126.79, 123.58, 122.17, 108.69, 58.37, 54.28, 52.40, 44.02, 43.58, 27.78, 23.45. \(\text{EI–MS} m/z\) (%) 919 (M\(^+\), 1%), 862 (5), 813 (3), 756 (50), 709 (12), 662 (25), 647 (24), 629 (12), 601 (16), 575 (49), 551 (51), 537 (39), 523 (56), 404 (18), 354 (28), 313 (22), 261 (18), 236 (25), 195 (17), 118 (27), 106 (27), 91 (100), 65 (18). \(\text{HRMS} m/z\) Found 941.4114, Calcd. for C\(_{28}\)H\(_{62}\)N\(_4\)O\(_4\)Na\(_2\) [M+Na]\(^+\) 941.4110.

### 3.14.2 13c → 13d

**Meso-isomer:** sulfanamide (13c: 257 mg, 0.28 mmol) was dissolved in methanol (6 mL). To this mixture was added an aqueous solution of HCl (4 N, 0.21 mL, 0.84 mmol, dissolved in methanol (6 mL). To this mixture was added and the resulting mixture was stirred at 80 °C under argon for 6 h. After cooling to room temperature then 0 °C, a solution of anhydrous t-BuOOH (~3.0 M in toluene, 1.0 mL, 3 mmol, 1.5 eq.) was added and the resulting mixture was stirred at 0 °C (ca. 5 h). Saturated aqueous solution of NH\(_4\)Cl (0.5 mL) was added. After 10 min, anhydrous sodium sulfate (ca. 2–3 g) was added. The resulting mixture was then filtered and washed with ethyl acetate (3 × 5 mL). After removal of the solvent, the residue was chromatographed on silica gel (dichloromethane:petroleum ether = 1:1) to afford the minor product (19b, 276 mg, 28 %) as white plates. Further elution afforded the major product (19c, 489 mg, 51 %) as a yellow solid.

### 3.15.1 19

m.p. 125–127 °C. \(R_f\) 0.54 (petroleum ether:ethyl acetate = 1:1). \(\text{FTIR}\) (KBr, thin film) cm\(^{-1}\) 3321, 3057, 2958, 2866, 1722, 1611, 1460, 1359, 1273, 1174, 1068, 928, 743, 704, 633, 596, 464. \(^{1}H\)-NMR (as a mixture of rotamers, 400 MHz, CDCl\(_3\), δ (ppm) 7.30–7.11 (12H, m), 7.08 (0.5H, t, J = 7.6 Hz), 7.07 (0.5H, t, J = 7.6 Hz), 6.92 (0.5H, t, J = 7.6 Hz), 6.91 (0.5H, t, J = 7.6 Hz), 6.61 (0.5H, d, J = 7.6 Hz), 6.60 (0.5H, d, J = 7.6 Hz), 5.07 (0.5H, s), 5.04 (0.5H, s), 4.86 (0.5H, d, J = 15.6 Hz), 4.83 (0.5H, d, J = 15.6 Hz), 4.61 (0.5H, d, J = 15.6 Hz), 4.59 (0.5H, d, J = 15.6 Hz), 4.19 (0.5H, d, J = 15.6 Hz), 4.17 (0.5H, d, J = 15.6 Hz), 4.02 (0.5H, d, J = 15.6 Hz), 4.01 (0.5H, d, J = 15.6 Hz), 3.28–2.95 (1H, m), 2.93–2.70 (1H, m), 1.28–1.23 (1H, m), 1.10 (4.5H, s), 1.09 (4.5H, s).

\(^{13}C\)-NMR (rotamer in brackets, 100 MHz, CDCl\(_3\), δ (ppm) 177.54, 141.86, 136.62 (136.56), 135.29, 129.86 (129.80), 129.21, 128.60, 128.36 (128.30), 127.41 (127.20), 127.03 (127.00), 123.73 (123.68), 122.88, 109.24, 74.75 (74.71), 57.97, 51.24, 43.46, 42.72, 36.55 (36.43), 23.09. \(\text{HRMS} m/z\) Found 499.2028, Calcd. for C\(_{28}\)H\(_{27}\)N\(_2\)O\(_4\)S [M+Na]\(^+\) 499.2031.
3.15.2 19b

m.p. 113–115 °C. \( R_t \) 0.52 (petroleum ether:ethyl acetate = 2:1). \textit{FTIR} (KBr, thin film) cm\(^{-1}\) 3415, 3059, 2980, 2930, 1718, 1612, 1462, 1360, 1310, 1172, 1124, 996, 934, 743, 702, 645, 521. \( ^1^H\)-NMR (as a mixture of rotamers, 400 MHz, CDCl\(_3\)), \( \delta \) (ppm) 7.39–7.10 (12H, m), 6.95 (1H, \( t, J = 7.6 \) Hz), 6.63 (1H, \( t, J = 7.6 \) Hz), 4.90 (0.4H, \( d, J = 16.0 \) Hz), 4.89 (0.6H, \( d, J = 16.0 \) Hz), 4.62 (0.4H, \( d, J = 15.6 \) Hz), 4.61 (0.6H, \( d, J = 15.6 \) Hz), 4.51–4.37 (1H, brs), 4.05 (0.4H, s), 3.99 (0.6H, s), 3.32–3.11 (2H, \( m \)), 2.27–2.15 (2H, \( m \)), 1.40 (4.5H, s), 1.39 (4.5H, s). \( ^{13}^C\)-NMR (100 MHz, CDCl\(_3\)), \( \delta \) (ppm) 177.44, 141.95, 136.04, 135.31, 129.61, 129.37, 128.82, 128.57, 127.79, 127.66, 127.15, 123.77, 123.18, 109.52, 74.81, 71.62, 52.20, 43.69, 42.52, 36.79, 24.79. \textit{HRMS} m/z: Found 515.1974, Calcd. for C\(_{28}\)H\(_{32}\)N\(_2\)NaO\(_4\)S \([M+Na]^+\) 515.1975.

3.16 Synthesis of Compound 21a

To a mixture of copper iodide (Cul, 190 mg, 1.0 mmol, 0.1 eq.) and \( \delta \)-iodoaniline 12c (6.14 g, 10.0 mmol) in anhydrous toluene (200 mL) was added a solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 20 mL, 20 mmol, 2.0 eq.). The resulting mixture was degassed and purged with argon (three times). The reaction mixture was then allowed to stir at 60 °C (oil bath) under argon for 5 h. After cooling to room temperature then to 0 °C, a solution of anhydrous \( t \)-BuOOH (degassed and purged with argon, \( \sim 3.0 \) M in toluene, 5.0 mL, 15 mmol, 1.5 eq.) was added. The reaction mixture was then stirred at 0 °C under argon for 3 h. Saturated aqueous solution of Na\(_2\)S\(_2\)O\(_3\) (10 mL) was added followed by saturated aqueous solution of NH\(_4\)Cl (10 mL). After 30 min, the resulting mixture was diluted with water (200 mL) and extracted with ethyl acetate (3 \( \times \) 100 mL). The combined organic phases were dried over anhydrous Na\(_2\)SO\(_4\). After removal of the solvents, the residue was chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 2:1) to afford the major product 21a (2.42 g, 50 %) as a pale yellow syrup. Further elution afforded the meso-isomer 21c, characterized after removal of tert-butylsulfinyl group, 0.205 g, 4.2 %), followed by minor product 21b, characterized after removal of the tert-butylsulfinyl group, 0.40 g, 8.2 %) as a pale yellow oil.

3.16.1 21a (Major Isomer)

\[ \delta^{{31}P}_{\text{CDCl}_3} = -153 \text{ (c 0.18, CHCl}_3\text{).} \]

\( R_t \) 0.42 (petroleum ether:ethyl acetate = 1:1). \textit{FTIR} (KBr, thin film) cm\(^{-1}\) 3420, 3061, 2925, 2843, 2357, 1712, 1608, 1482, 1460, 1358, 1175, 1110, 991, 921, 743, 701. \( ^1^H\)-NMR (400 MHz, CDCl\(_3\)), \( \delta \) (ppm) 7.50–6.31 (2 \( \times \) 14H, \( m \)), 5.62–5.46 (2 \( \times \) 1H, \( m \)), 5.10–4.72 (2 \( \times \) 2.35H, \( m \)), 4.56 (2 \( \times \) 0.33H, \( d, J = 16.0 \) Hz), 4.44 (2 \( \times \) 0.33H, \( d, J = 15.6 \) Hz), 4.33 (2 \( \times \) 0.67H, \( dd, J = 11.6, 15.6 \) Hz), 4.03 (2 \( \times \) 0.33H, \( d, J = 15.6 \) Hz), 3.66 (2 \( \times \) 0.33H, \( d, J = 13.2 \) Hz), 3.55 (2 \( \times \) 0.33H, \( d, J = 13.2 \) Hz), 3.49 (2 \( \times \) 0.33H, \( d, J = 12.8 \) Hz), 3.43–3.31 (2 \( \times \) 0.67H, \( m \)), 3.14 (2 \( \times \) 0.33H, \( d, J = 13.2 \) Hz), 3.02 (2 \( \times \) 0.33H, \( d, J = 13.2 \) Hz), 2.91–2.80 (2 \( \times \) 0.33H, \( m \)), 2.77 (2 \( \times \) 0.33H, \( d, J = 12.8 \) Hz), 2.67–2.50 (2 \( \times \) 1H, \( m \)), 2.50–2.38 (2 \( \times \) 0.67H, \( m \)), 2.22–2.14 (2 \( \times \) 0.33H, \( m \)), 0.97 (2 \( \times \) 1H, \( brs \)). \( ^{13}^C\)-NMR (rotamer in brackets, 100 MHz, CDCl\(_3\)), \( \delta \) (ppm) 179.54 (179.21), 143.82 (143.70), 141.22...

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3.16.5 21e → 21e (Meso-isomer)

Sulfinamide (21c: 205 mg, 0.21 mmol) was dissolved in methanol (6 mL). To this mixture was added an aqueous solution of HCl (4 N, 0.16 mL, 0.63 mmol, 3 eq.). The resulting mixture was allowed to stir at room temperature under nitrogen for 1 h. The reaction mixture was then treated with saturated aqueous solution of sodium bicarbonate (~4 mL) and concentrated under reduced pressure. The mixture was diluted with water (10 mL) and extracted with dichloromethane (3 × 5 mL), the combined organic phases were dried over anhydrous Na2SO4. After removal of the solvents, the residue was chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 1:2) to afford the diamine (21e) (145 mg, 91 %) as yellow syrup.

3.17 Synthesis of Compound 22

A solution of 21a (485 mg, 0.5 mmol) in dichloromethane and methanol (20 mL, 1:1 mixture) was cooled to −78 °C (dry ice–acetone bath). Ozone was then passed through the solution for 10 min. The reaction progress was monitored by TLC. Sodium borohydride (189 mg, 5 mmol, 10 eq.) was added. The reaction mixture was then gradually warmed up to room temperature under argon at stirring overnight. Saturated aqueous solution of NH4Cl (10 mL) was added. The resulting mixture was diluted with water (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried over anhydrous Na2SO4. After removal of the solvents, the residue was chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 1:2) to afford the product (22, 401 mg, 82 %) as a pale yellow syrup.

[\text{z}]_{D}^{20} = -332 (c 0.14, CHCl3). Rf 0.45 (petroleum ether:ethyl acetate = 1:2). FTIR (KBr, thin film) cm⁻¹ 3730, 3436, 2921, 2351, 1703, 1609, 1460, 1364, 1174, 1046, 745. 1H-NMR (400 MHz, CDCl3), δ (ppm) 7.27–7.01 (2 × 9H, m), 4.96–4.60 (2 × 4H, m), 4.68 (2 × 0.5H, d, J = 8.0 Hz), 6.45 (2 × 0.5H, d, J = 8.0 Hz), 5.56–5.35 (2 × 1H, m), 4.98 (2 × 0.5H, d, J = 16.0 Hz), 4.87 (2 × 0.5H, d, J = 10.0 Hz), 4.76 (2 × 0.5H, d, J = 15.6 Hz), 4.68 (2 × 0.5H, d, J = 16.8 Hz), 4.54 (2 × 0.5H, d, J = 16.8 Hz), 4.32 (2 × 0.5H, brs), 3.88 (2 × 0.5H, brs), 3.55 (2 × 0.5H, d, J = 13.2 Hz), 3.49 (2 × 0.5H, d, J = 13.2 Hz), 3.13 (2 × 0.5H, d, J = 13.2 Hz), 3.01 (2 × 0.5H, d, J = 13.2 Hz), 3.00 (2 × 0.5H, brs), 2.92 (2 × 1H, brs), 2.68–2.50 (2 × 2H, m), 0.97 (2 × 1H, brs). 13C-NMR (rotamer in brackets, 100 MHz, CDCl3), δ (ppm) 178.05 (176.96), 145.05 (144.20), 140.49 (140.39), 140.31 (140.19), 136.17 (135.85), 128.56 (128.44), 128.22 (128.00), 127.55, 127.25 (127.21), 126.95, 126.69 (126.56), 125.10, 124.54, 121.74 (121.45), 115.99 (115.44), 109.41 (109.30), 58.75 (58.56), 55.83 (55.34), 50.92 (50.85), 44.37, 37.69 (36.62). HRMS m/z Found 763.4003, Calcd. for C28H31N3O2 [M+H]+: 763.4012.
To a mixture of copper iodide (CuI, 190.4 mg, 1.0 mmol, 1 eq.) and bromoanilide 12b′ (5.41 g, 10 mmol) in anhydrous toluene (200 mL) was added a solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 20 mL, 20 mmol, 2 eq.). The resulting mixture was degassed and purged with argon (three times). After which, the reaction mixture was stirred at 80 °C (oil bath) for 5 h. After cooling to room temperature then to 0 °C, a solution of anhydrous r-BuOOH (~3 M in toluene, 5.0 mL, 15 mmol, 1.5 eq.) was added. The reaction mixture was allowed to stir at 0 °C under argon for 3 h. Saturated aqueous solution of NH4Cl (10 mL) was added. After 30 min, the mixture was diluted with water (200 mL). The resulting mixture was then extracted with ethyl acetate (3 × 100 mL). The combined organic phases were dried over anhydrous Na2SO4. After removal of the solvents, the residue was chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 1:1 → 1:2 → 1:3) to afford the major product (13a′ + 13b′, 3.59 g, 78 %) as a pale yellow syrup. Further elution afforded the minor product (13c′, 0.32 g, 7 %) as a pale yellow oil, which was characterized after removal of tert-butylsulfanyl group (see 13d).

3.19.1 13a′ + 13b′

A mixture of diastereomers at C3–C3′ position (84:16): Rf 0.45 (petroleum ether:ethyl acetate = 1:1). FTIR (KBr, thin film) cm−1 3429, 2969, 2352, 1702, 1612, 1456, 1365, 1052. 1H-NMR (400 MHz, CDCl3, major C3R–C3′R-isomer reported), δ (ppm) 7.37–7.19 (2 × 8H, m), 7.10–7.03 (2 × 2H, m), 6.81 (2 × 1H, t, J = 7.6 Hz), 6.68 (2 × 1H, d, J = 7.6 Hz), 6.49 (2 × 1H, t, J = 7.6 Hz), 6.26 (2 × 1H, d, J = 8.0 Hz), 5.91 (2 × 1H, d, J = 15.6 Hz), 4.36 (2 × 1H, d, J = 15.6 Hz), 4.21 (2 × 2H, s), 3.11 (2 × 1H, ddd, J = 4.4, 12.4, 12.8 Hz), 2.37 (2 × 1H, ddd, J = 3.6, 13.2, 13.6 Hz), 2.22–2.10 (2 × 1H, m), 1.17 (2 × 9H, s). 13C-NMR (100 MHz, CDCl3, major C3R–C3′R-isomer reported), δ (ppm) 176.63, 142.44, 137.01, 135.32, 128.96, 128.81, 128.34, 127.70, 127.64, 127.45, 126.80, 126.72, 123.52, 122.11, 108.63, 58.31, 54.22, 52.40, 43.96, 43.51, 27.70, 23.40. EI–MS m/z (%) 919 (M+1, 1 %), 918 (1 %), 706 (2), 588 (3), 575 (1), 354 (3), 249 (2), 236 (4), 223 (4), 132 (10), 118 (19), 106 (7), 91 (100), 65 (5). HRMS m/z Found 918.4422, Calcd. for C56H58N4O8S2 (M)+ 918.4213; Found 919.4307, Calcd. for C56H62N4O4S2 [M+H]+ 919.4291.

## 4 Synthesis of Compound 24

Sulfinamide (13a′ + 13b′; 3.59 g, 3.9 mmol) was dissolved in methanol (60 mL). To this mixture was added an aqueous solution of HCl (4 N, 2.9 mL, 11.7 mmol, 3 eq.). The resulting mixture was allowed to stir at room temperature under nitrogen for 1 h. The reaction mixture was then treated with saturated aqueous solution of sodium bicarbonate (~50 mL) and concentrated under reduced pressure. The mixture was diluted with water (100 mL) and extracted with dichloromethane (3 × 50 mL), the combined organic phases were dried over anhydrous Na2SO4. After removal of the solvent, the residue was chromatographed on silica gel (dichloromethane:methanol = 20:1) to afford the amine (24) (2.63 g, 95 %) as white foam. The diamine was dissolved in methanol (20 mL) and HCl (2 N, 5.6 mL, 11.1 mmol, 3.0 eq.) was added. This solution was allowed to crystallize at room temperature. The needle-like crystals were collected and subjected to HPLC analysis (a 1:1 mixture of C3R–C3′R and C3S–C3′S enantiomers). The mother liquid was then treated with saturated aqueous solution of sodium bicarbonate to pH 8, and extracted with dichloromethane (3). The combined organic phases were dried over anhydrous Na2SO4. After removal of the solvents, the enantiomeric pure product 24 was obtained (1.60 g, 61 %) as a pale yellow syrup.
(2 × 1H, t, J = 7.6 Hz), 6.39 (2 × 1H, d, J = 7.6 Hz), 5.03 (2 × 1H, d, J = 15.6 Hz), 4.45 (2 × 1H, d, J = 15.6 Hz), 3.60 (2 × 1H, d, J = 13.6 Hz), 3.53 (2 × 1H, d, J = 13.6 Hz), 3.26 (2 × 1H, ddd, J = 5.6, 6.0, 13.2 Hz), 2.64 (2 × 1H, ddd, J = 7.6, 8.0, 13.2 Hz), 2.27–2.17 (2 × 2H, m). $^{13}$C-NMR (100 MHz, CDCl$_3$), $\delta$ (ppm) 178.03, 143.09, 140.31, 135.85, 128.68, 128.32, 128.06, 128.01, 127.85, 127.58, 126.74, 124.12, 121.76, 108.52, 55.14, 53.65, 45.41, 44.12, 29.22. EI–MS m/z (%): 710 (M$^+$, 2%), 577 (1), 356 (4), 344 (2), 262 (3), 236 (4), 223 (4), 134 (8), 118 (12), 106 (21), 91 (100). HRMS m/z found 710.3622, Calcd. for C$_{48}$H$_{46}$N$_4$O$_2$ [M]$^+$ 710.3621.

4.1 Synthesis of Compound 25

To diamine 24 (0.82 g, 1.15 mmol) in acetonitrile (10 mL) was a solution of formaldehyde (37 % aqueous solution, 0.44 mL, 5.75 mmol, 5.0 eq.) was added and the reacting mixture was stirred at room temperature under argon for 2 h. A solution of methanol in dichloromethane (MeOH:CH$_2$Cl$_2$ = 5:95, 10 mL) saturated with ammonia was added. The mixture was then allowed to stir at room temperature for 5 min. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (dichloromethane:MeOH:NH$_3$–H$_2$O = 300:10:1) to afford the product (25, 0.82 g, 96 % yield) as a pale yellow syrup.

$\left[\alpha\right]_{D}^{20} +171 (c$ 0.10, MeOH). R$_t$ 0.45 (CH$_2$Cl$_2$:MeOH = 30:1). FTIR (KBr, thin film) cm$^{-1}$ 3431, 2970, 2352, 1628, 1397, 1089. $^1$H-NMR (400 MHz, CDCl$_3$), $\delta$ (ppm) 7.32–7.11 (2 × 5H, m), 7.03 (2 × 1H, d, J = 7.2 Hz), 6.92 (2 × 1H, dt, $d$ = 0.8, 7.6 Hz), 6,70 (2 × 1H, t, J = 7.6 Hz), 6.35 (2 × 1H, d, J = 7.6 Hz), 5.10 (2 × 1H, d, J = 15.6 Hz), 4.40 (2 × 1H, d, J = 15.6 Hz), 3.25–3.13 (2 × 1H, m), 2.58–2.49 (2 × 1H, m), 2.21 (2 × 3H, s), 2.12–2.03 (2 × 3H, m). $^{13}$C-NMR (100 MHz, CDCl$_3$), $\delta$ (ppm) 177.73, 142.98, 135.88, 128.74, 128.20, 128.00, 127.86, 127.66, 124.02, 121.84, 108.54, 55.04, 47.81, 44.05, 36.12, 29.00. EI–MS m/z (%): 558 (M$^+$, 21 %), 526 (5), 501 (100), 470 (12), 444 (43), 280 (52), 248 (7), 236 (38), 223 (28), 187 (7), 158 (13), 91 (56). HRMS m/z found 558.2989, Calcd. for C$_{39}$H$_{38}$N$_4$O$_2$ [M]$^+$ 558.2995.

4.3 Synthesis of Compound 27

Diamine 26 (558 mg, 1.0 mmol) in THF (25 mL) was degassed and purged with argon (three times). A solution of diisobutylaluminium hydride (DIBAL–H, 1.1 M in THF, 10 mL, 10 mmol, 10.0 eq.) was added and the reacting mixture was stirred at 0 °C for 1 h, then at room temperature for 2 h and finally at 80 °C (oil bath) under argon for 15 h. After cooling to room temperature, a saturated aqueous solution of potassium sodium tartrate (10 mL) was added and the reacting mixture was stirred at room temperature for 2 h. The mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were dried over anhydrous sodium sulfate. After filtration and removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (petroleum ether ether 60–90 °C:ethyl acetate = 1:4) to afford the product (27, 284 mg, 54 % yield) as white foam.

$\left[\alpha\right]_{D}^{20} +248 (c$ 0.11, CHCl$_3$). R$_t$ 0.54 (petroleum ether–ethyl acetate = 1:4). FTIR (KBr, thin film) cm$^{-1}$ 3419, 3029, 2919, 2791, 1598, 1488, 1350, 1258, 1147, 1039, 736. $^1$H-NMR (400 MHz, CDCl$_3$), $\delta$ (ppm) 7.31–7.21 (2 × 4H,
4.4 Synthesis of (+)-Chimonanthine

To a solution of liquid ammonia (freshly distilled and collected by Birch condenser, acetone–dry ice, 50–60 mL) at −78 °C was added sodium metal (ca. 124 mg, 5.4 mmol, 10 eq.). A solution of chimonanthine precursor (27, 284 mg, 0.54 mmol) in anhydrous THF (10 mL) was added to this dark blue solution of liquid ammonia. After stirring at −78 °C for 15 min, a powder of NH 4Cl (433 mg, 8.1 mmol) was added in one portion followed by saturated aqueous solution of NH 4Cl (5 mL). The resulting mixture was allowed to evaporate in fume hood. The residue was then diluted with water (20 mL) and extracted with dichloromethane (3 × 20 mL). The organic phases were combined and dried over anhydrous sodium sulfate. After filtration, the solvent was removed under reduced pressure and the crude product was chromatographed on silica gel (CH 2Cl 2:MeOH:NH 3·H 2O = 200:10:1) to afford the product (2, 177 mg, 95 %) as white plates.

m.p. 170−172 °C, [α] D 20 +285 (c 0.12, EtOH). R f 0.48 (CH 2Cl 2:MeOH:NH 3·H 2O = 200:10:1). FTIR (KBr, thin film) cm −1 3404, 3219, 2930, 2856, 2797, 1601, 1480, 1252, 1161, 1031, 739, 648. 1 H-NMR (300 MHz, CDCl 3), δ (ppm) 7.19 (2 × 1H, d, J = 7.2 Hz), 6.99 (2 × 1H, t, J = 7.2 Hz), 6.67 (2 × 1H, t, J = 7.2 Hz), 6.54 (2 × 1H, d, J = 7.2 Hz), 4.34 (2 × 1H, brs), 4.12 (2 × 1H, brs), 2.63–2.48 (2 × 3H, m), 2.30 (2 × 3H, s), 2.18–2.01 (2 × 1H, m). 13 C-NMR (75 MHz, CDCl 3), δ (ppm) 150.74, 133.27, 128.27, 124.58, 118.78, 109.41, 85.40, 63.41, 52.83, 37.38, 35.66. EI–MS m/z (%) 346 (M +, 7 %), 302 (2), 259 (2), 245 (3), 231 (3), 190 (11), 173 (37), 172 (100), 157 (6), 143 (8), 130 (30), 117 (6), 103 (5), 85 (24), 83 (28). HRMS m/z Found 346.2151, Calcd. for C 22 H 33 N 4 [M] + 346.2157.

4.5 Synthesis of (+)-Folicantheme

To a solution of amine 2 (35 mg, 0.1 mmol) in acetonitrile (3 mL) was added a solution of formalin (37 % HCHO in water, 39 μL, 0.52 mmol, 5.2 eq.) and sodium triacetoxyborohydride [NaBH(OAc) 3, 110 mg, 0.52 mmol]. The resulting mixture was then stirred at room temperature under argon for 1 h. The mixture was then treated with a solution of methanol in dichloromethane saturated with ammonia (ca. 5 mL, CH 2Cl 2:MeOH = 95:5). After stirring for 5 min, the mixture was concentrated and the residue was chromatographed on silica gel (dichloromethane: methanol:NH 3·H 2O = 500:10:1) to afford the product (3, 35.5 mg, 95 %) as white plates.

m.p. 183−185 °C, [α] D 20 +315 (c 0.10, MeOH). R f 0.48 (CH 2Cl 2:MeOH:NH 3·H 2O = 200:10:1). FTIR (KBr, thin film) cm −1 3434, 2944, 2784, 1601, 1488, 1345, 1156, 1034, 730. 1 H-NMR (300 MHz, CDCl 3), δ (ppm) 7.02–6.88 (2 × 2H, m), 6.50 (2 × 1H, t, J = 7.5 Hz), 6.26 (2 × 1H, d, J = 7.5 Hz), 4.38 (2 × 1H, brs), 3.00 (2 × 3H, s), 2.70–2.58 (2 × 1H, m), 2.51–2.33 (2 × 2H, m), 2.41 (2 × 3H, s), 2.04–1.91 (2 × 1H, m). 13 C-NMR (75 MHz, CDCl 3), δ (ppm) 153.00, 132.95, 128.14, 123.70, 116.71, 105.90, 92.03, 62.74, 52.72, 38.03, 35.52, 35.39. EI–MS m/z (%) 374 (M +, 11 %), 273 (2), 187 (45), 186 (100), 172 (9), 157 (8), 145 (14), 144 (31), 130 (7), 115 (5), 85 (19), 83 (22). HRMS m/z Found 374.2480, Calcd. for C 24 H 30 N 4 [M] + 374.2470.

4.6 Synthesis of (−)-Calycantheme

To a solution of acetic acid in D 2O (0.43 M, 4 mL) was added chimonanthine 2 (35 mg, 0.1 mmol). The resulting mixture was then stirred at 95 °C for 18 h under an atmosphere of argon. After cooling down to room temperature, the mixture was diluted with dichloromethane (10 mL) and treated with a saturated aqueous solution of sodium bicarbonate (until pH 8). The combined aqueous phases were back-extracted with dichloromethane (3 × 8 mL). The organic phases were combined and dried over anhydrous sodium sulfate. After filtration and removal of the solvent, the residue was chromatographed on silica gel (dichloromethane:methanol:NH 3·H 2O = 500:10:1) to afford the product (4, 18 mg, 52 %) as a white solid.

m.p. 232−235 °C, [α] D 20 −615 (c 0.15, EtOH). FTIR (KBr, thin film) cm −1 3435, 2968, 1627, 1451, 1047, 608. 1 H-NMR (300 MHz, CDCl 3), δ (ppm) 7.01 (2 × 1H, d, J = 7.5 Hz), 6.82 (2 × 1H, t, J = 7.5 Hz), 6.55 (2 × 1H, t, J = 7.5 Hz), 6.28 (2 × 1H, d, J = 7.5 Hz), 4.69 (2 × 1H, brs), 4.44 (2 × 1H, s), 3.17 (2 × 1H, ddd, J = 5.4, 13.2, 13.2 Hz), 2.70 (2 × 1H, dd, J = 4.6, 11.4 Hz), 2.46 (2 × 3H, s), 2.29 (2 × 1H, ddd, J = 3.6, 11.4, 11.4 Hz), 1.33 (2 × 1H, ddd, J = 3.6, 13.2 Hz). 13 C-NMR (75 MHz, CDCl 3), δ (ppm) 145.00, 126.88, 124.58, 116.90, 112.36, 71.37, 46.63, 42.50, 35.96, 31.55. EI–MS m/z (%) 347 (M ++H, 31 %), 346 (M +, 100 %), 314 (5), 302 (18), 288 (29), 270 (23), 259 (13), 245 (28), 231 (59), 219 (11), 199 (9), 185 (13), 172 (21), 149 (30), 143 (27), 134.9. X. Shen et al.
4.7 Synthesis of Compound 28

To a solution of sulfamidine 21a (2.42 g, 2.5 mmol) in methanol (50 mL) was added an aqueous solution of HCl (4 N, 1.88 mL, 7.5 mmol, 3 eq.). The resulting mixture was allowed to stir at room temperature for 1 h. The reaction mixture was then treated with saturated aqueous solution of sodium bicarbonate (until pH 8) and concentrated under reduced pressure. The mixture was diluted with water (80 mL) and extracted with dichloromethane (3 × 50 mL), the combined organic phases were dried over anhydrous Na2SO4. After removal of the solvents, the residue was chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 7:1) to afford the amine (28) (1.81 g, 95 %) as a pale yellow syrup.

$[\delta^2_{D}]$−241 (c 0.18, CHCl3). ee = 99.8 %, $R_1$ 0.65 (petroleum ether:ethyl acetate = 2:1). FTIR (KBr, thin film) cm$^{-1}$ 3454, 3061, 2921, 1699, 1609, 1361, 742. $^1$H-NMR (400 MHz, CDCl3), δ (ppm) 7.23–7.15 (2 × 5H, m), 7.11–7.04 (2 × 3H, m), 6.98 (2 × 1H, t, $J = 6.8$ Hz), 6.97 (2 × 1H, d, $J = 7.2$ Hz), 6.72–6.66 (2 × 2H, m), 6.61 (2 × 1H, t, $J = 7.2$ Hz), 6.35 (2 × 1H, t, $J = 8.0$ Hz), 5.52 (2 × 1H, $ddd$, $J = 8.4$, 10.0, 17.2 Hz), 5.00 (2 × 1H, $d$, $J = 10.0$ Hz), 4.75 (2 × 1H, d, $J = 17.2$ Hz), 4.48 (2 × 1H, d, $J = 15.6$ Hz), 4.42 (2 × 1H, d, $J = 15.6$ Hz), 3.50 (2 × 1H, $d$, $J = 13.2$ Hz), 3.33 (2 × 1H, $dd$, $J = 4.0$, 13.6 Hz), 3.01 (2 × 1H, d, $J = 13.2$ Hz), 2.54 (2 × 1H, $ddd$, $J = 4.0$, 8.6, 10.8 Hz), 2.40 (2 × 1H, $dd$, $J = 10.8$, 13.6 Hz), 0.91 (2 × 1H, brs). $^{13}$C-NMR (100 MHz, CDCl3), δ (ppm) 179.28, 143.86, 140.53, 140.01, 136.12, 128.44, 128.07, 128.02, 127.87, 127.70, 127.31, 126.32, 124.88, 121.36, 115.53, 108.44, 57.58, 54.78, 50.31, 44.45, 34.85. +TOF-MS m/z (%) 763 (M$^+$+1, 100 %), 382 (15), 275 (2), 236 (20). HRMS m/z Found 763.4015, Calcd. for C$_{28}$H$_{43}$Cl$_{2}$N$_{2}$O$_{2}$ [M+H]$^+$ 763.4012.

4.8 Synthesis of Compound 28a

To a solution of dichloroamine 28a (789 mg, 0.95 mmol) in anhydrous THF (20 mL) was added a powder of potassium tert-butoxide (t-BuOK, 320 mg, 2.85 mmol, 3.0 eq.). The resulting mixture was stirred at 0 °C for 1 h. After which, the reaction mixture was treated with a solution of saturated NH$_4$Cl (5 mL). After removal of the solvents, the residue was diluted with water (25 mL) and extracted with dichloromethane (3 × 25 mL), and the combined organic phases were dried over anhydrous Na$_2$SO$_4$. After filtration and removal of the solvent under reduced pressure, the crude product was obtained (670 mg, 93 % yield) as pale yellowish oil. The crude imine was dissolved in ethanol (29 mL), and the combined organic phases was dried over anhydrous Na$_2$SO$_4$. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 7:1) to afford the product (28a, 789 mg, 95 % yield) as a pale yellow syrup.

$[\delta^2_{D}]$−278 (c 0.50, CHCl3). $R_1$ 0.45 (petroleum ether:ethyl acetate = 7:1). FTIR (KBr, thin film) cm$^{-1}$ 3362, 3055, 1702, 1607, 1486, 1360, 1170, 997, 916, 751. $^1$H-NMR (400 MHz, CD$_3$OD), δ (ppm) 7.51 (2 × 2H, $d$, $J = 7.6$ Hz), 7.43–7.33
(2 × 3H, m), 7.05 (2 × 1H, d, J = 8.0 Hz), 7.02 (2 × 1H, t, J = 7.6 Hz), 6.77 (2 × 1H, t, J = 7.6 Hz), 6.61 (2 × 1H, d, J = 8.0 Hz), 5.50 (2 × 1H, ddd, J = 7.2, 10.4, 17.2 Hz), 5.18 (2 × 1H, d, J = 15.6 Hz), 4.64–4.53 (2 × 3H, m), 3.31 (2 × 1H, ddd, J = 6.8, 13.6 Hz), 2.93 (2 × 1H, ddd, J = 6.4, 13.2 Hz), 2.59 (2 × 1H, ddd, J = 6.8, 13.6 Hz).\(^{13}C\)-NMR (100 MHz, CD\(_3\)OD), \(\delta\) (ppm) 179.10, 144.37, 142.14, 137.21, 129.64, 129.46, 128.76, 128.60, 125.45, 122.76, 114.37, 109.83, 56.14, 52.99, 45.11, 36.86. EI–MS \(m/z\) (%) 583 (M\(^+\) + 1, 11 %), 513 (20), 496 (7), 444 (4), 292 (76), 291 (24), 275 (12), 261 (6), 236 (100), 235 (58), 223 (7), 206 (4), 158 (15), 130 (7), 91 (100). HRMS \(m/z\) Found 582.2991, Calcd. for C\(_{38}\)H\(_{38}\)N\(_4\)O\(_2\) [M\(^+\)] 582.2995.

4.10 Synthesis of Compound 30

Diamine 29 (291 mg, 0.5 mmol) in THF (20 mL) was degassed and purged with argon (three times). A solution of diisobutylaluminium hydride (DIBAL-H, 1.0 M in THF, 5 mL, 5 mmol, 10.0 eq.) was added at 0 °C and the resulting mixture was stirred at 0 °C for 1 h, then at room temperature for 2 h and finally at 80 °C (oil bath) under argon for 15 h. After cooling to room temperature, a saturated aqueous solution of potassium sodium tartrate (5 mL) was added and the resulting mixture was stirred at room temperature for 2 h. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried over anhydrous sodium sulfate. After filtration and removal of the solvent, the residue was chromatographed on silica gel (petroleum ether 60–90 °C/ethyl acetate = 3:1) to afford the product (30, 143 mg, 52 % yield) as a yellow oil.

\([\delta]_{D}^{20} = -310\) (c 0.18, MeOH). \(R_t\) 0.56 (petroleum ether–ethyl acetate = 3:1). FTR (KBr, thin film) cm\(^{-1}\) 3437, 2919, 1601, 1491, 1349, 1088, 909, 738. \(^1H\)-NMR (400 MHz, CDCl\(_3\)), \(\delta\) (ppm) 7.30–7.12 (2 × 5H, m), 7.03 (2 × 1H, d, J = 7.2 Hz), 6.92 (2 × 1H, t, J = 7.2 Hz), 6.48 (2 × 1H, t, J = 7.2 Hz), 6.20 (2 × 1H, d, J = 8.0 Hz), 5.64 (2 × 1H, ddd, J = 6.8, 10.4, 17.2 Hz), 5.00 (2 × 1H, d, J = 17.2 Hz), 4.92 (2 × 1H, d, J = 10.4 Hz), 4.76 (2 × 1H, s), 4.38 (2 × 1H, d, J = 16.0 Hz), 4.31 (2 × 1H, d, J = 16.0 Hz), 3.40–3.30 (2 × 1H, m), 2.10–1.97 (2 × 2H, m), 1.70 (2 × 1H, brs).

\(^{13}C\)-NMR (100 MHz, CDCl\(_3\)), \(\delta\) (ppm) 152.27, 139.11, 139.00, 131.43, 128.71, 128.60, 127.54, 127.20, 124.61, 116.56, 115.58, 105.21, 85.91, 62.82, 59.74, 49.15, 44.84. EI–MS \(m/z\) (%) 550 (M\(^+\), 10 %), 308 (3), 274 (100), 259 (3), 236 (3), 220 (19), 183 (18), 169 (5), 130 (7), 118 (6), 91 (62). HRMS \(m/z\) Found 550.3096, Calcd. for C\(_{38}\)H\(_{38}\)N\(_4\) [M\(^+\)] 550.3096.

4.11 Synthesis of Compound 31

To a solution of diamine 31 (74 mg, 0.2 mmol) and FMOC-(S)-MePhe–OH (200 mg, 0.5 mmol, 2.5 eq.) in anhydrous DMF (3 mL) was added Et\(_3\)N (0.14 mL, 1 mmol, 5.0 eq.) and O-(7-azabenztiazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 190 mg, 0.5 mmol, 2.5 eq.) at 0 °C. The resulting mixture was then stirred at room temperature for 12 h. The mixture was then treated with an aqueous solution of LiCl (5 %, ca. 10 mL). After stirring for 5 min, the mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with 5 % aqueous solution of LiCl (5 mL) and dried over anhydrous sodium sulfate. After filtration, the solvent was removed under
reduced pressure to afford the product (32, 198 mg, 87 %) which was used directly in the next step without further purification. To a solution of olefin 32 (114 mg, 0.1 mmol) in THF (3 mL) and H2O (1 mL) was added 4-methylmorpholine-N-oxide (47 mg, 0.4 mmol, 4.0 eq.) and OsO4 (20 mg/mL in water, 0.13 mL, 0.01 mmol, 0.1 eq.). The resulting mixture was then stirred at room temperature for 20 h under nitrogen. After which, NaIO4 (86 mg, 0.4 mmol, 4.0 eq.) was added and the mixture was allowed to stir at room temperature for 3 h. The resulting mixture was then diluted with water (10 mL) and extracted with ethyl acetate (3 × 15 mL). The organic phases were combined and dried over anhydrous sodium sulfate. After filtration and removal of the solvent, the residue was chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 3:1) to afford the dialdehyde (33, 106 mg, 93 %) as white plates.

m.p. 155–157 °C, [α]D 20 = –318 (c 0.35, CHCl3). Rf 0.41 (petroleum ether:ethyl acetate = 3:1). FTIR (KBr, thin film) cm⁻¹ 3426, 2921, 1651, 1542, 1075, 749. 1H-NMR (400 MHz, CDCl3), δ (ppm) 8.95 (2 × 1H, d, J = 4.4 Hz), 7.78 (2 × 2H, d, J = 7.6 Hz), 7.58–7.00 (2 × 3H, t, J = 7.6 Hz), 6.63 (2 × 1H, t, J = 7.6 Hz), 6.32 (2 × 1H, d, J = 7.6 Hz), 5.12 (2 × 1H, t, J = 8.0 Hz), 4.92 (2 × 2H, s), 4.58 (2 × 1H, dd, J = 7.2, 10.4 Hz), 4.36 (2 × 1H, dd, J = 7.2, 10.4 Hz), 4.25 (2 × 1H, t, J = 6.8 Hz), 3.81–3.74 (2 × 1H, m), 3.12 (2 × 3H, s), 2.97–2.85 (2 × 2H, m), 2.08–2.00 (2 × 1H, m), 1.92–1.82 (2 × 1H, m). 13C-NMR (100 MHz, CDCl3), δ (ppm) 195.77, 170.75, 157.86, 149.38, 143.84, 143.66, 141.47, 135.72, 130.06, 129.08, 128.99, 128.03, 127.99, 127.71, 127.29, 126.22, 125.17, 125.08, 123.80, 120.24, 118.77, 109.18, 79.14, 68.60, 64.42, 62.14, 56.28, 47.23, 36.83, 32.84, 30.40. HRMS m/z Found 1141.4830, Calcd. for C27H66N6O8 [M+H]+ 1141.4864; Found 1163.4662, Calcd. for C72H66N6NaO8 [M+Na]+ 1163.4683.

4.13 Synthesis of (−)-Ditryptophenaline

To a solution of dialdehyde 33 (106 mg, 0.093 mmol) in THF (2 mL), water (2 mL) and t-BuOH (0.5 mL) was added 2-methyl-2-butene (1 mL), NaClO2 (80% purity, 105 mg, 0.93 mmol, 10 eq.) and KH2PO4 (253 mg, 1.86 mmol, 20 eq.). The resulting mixture was then stirred at room temperature for 15 h. After which, the mixture was diluted with a saturated aqueous solution of NH4Cl (40 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (10 mL) and dried over anhydrous sodium sulfate. After filtration and removal of the solvent, the crude product was obtained (101 mg, 93 %) and used in next step without further purification. The diacid (101 mg) was dissolved in THF (3 mL) and treated with piperidine (0.5 mL) at room temperature for 4 h. After removal of solvent and excess piperidine, the crude yellowish oil (60 mg) was obtained and used in next step without further purification. To a solution of aminoacid (60 mg, ~0.082 mmol) in dichloromethane (4 mL) was added DCC (169 mg, 0.82 mmol, 10 eq.). The resulting mixture was stirred at 40 °C for 15 h. After removal of the solvent, the residue was chromatographed on silica gel (petroleum ether 60–90 °C:ethyl acetate = 3:1 → 1:5) to afford the product (5, 50 mg, 78 % over three steps) as white plates.

m.p. 201–202 °C, [α]D 20 = –292 (c 0.40, CH2Cl2). Rf 0.41 (petroleum ether:ethyl acetate = 1:5). FTIR (KBr, thin film) cm⁻¹ 3426, 2921, 1651, 1542, 1075, 749. 1H-NMR (400 MHz, CDCl3), δ (ppm) 7.55 (2 × 2H, t, J = 7.6 Hz), 7.50 (2 × 1H, t, J = 7.2 Hz), 7.13 (2 × 2H, d, J = 7.2 Hz), 7.06 (2 × 1H, dt, J = 0.8, 7.6 Hz), 6.96 (2 × 1H, d, J = 7.6 Hz), 6.69 (2 × 1H, t, J = 7.2 Hz), 6.54 (2 × 1H, d, J = 7.6 Hz), 4.80 (2 × 1H, s), 4.68 (2 × 1H, s), 4.27–4.22 (2 × 1H, m), 3.65 (2 × 1H, dd, J = 4.8, 12.0 Hz), 3.52 (2 × 1H, dd, J = 3.0, 14.4 Hz), 3.24 (2 × 1H, dd, J = 4.4, 14.4 Hz), 3.02 (2 × 3H, s), 2.01 (2 × 1H, dd, J = 4.8, 12.4 Hz), 1.56 (2 × 1H, t, J = 12.4 Hz). 13C-NMR (100 MHz, CDCl3), δ (ppm) 165.55, 164.10, 150.30, 134.64, 129.78, 129.42, 129.46, 128.07, 126.62, 125.89, 119.08, 117.51, 89.05, 58.70, 36.34, 36.14, 32.69. HRMS m/z Found 693.3178, Calcd. for C42H41N6O4 [M+H]+ 693.3189.

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References

1. G.A. Cordell, J.E. Saxton, in The Alkaloids: Chemistry and Physiology, vol. 20, ed. by R.H.F. Manske, R.G.A. Rodrigo (Academic, New York, 1981), p. 3
2. T. Hino, M. Nakagawa, in The Alkaloids: Chemistry and Pharmacology, vol. 34, ed. by A. Brossi (Academic, San Diego, 1988), p. 1
74. B.M. Trost, M. Osipov, Angew. Chem. Int. Ed. 52, 9176 (2013)
75. S. Ghosh, S. Bhunia, B.N. Kakde, S. De, A. Bisai, Chem. Commun. 50, 2434 (2014)
76. G.B. Jones, B.J. Chapman, Synthesis 5, 475 (1995)
77. J.G. Ruano, A. Parra, V. Marcos, C. del Pozo, S. Catalán, S. Montenegro, S. Fustero, A. Poveda, J. Am. Chem. Soc. 131, 9432 (2009)
78. D.A. Cogan, G. Liu, J. Ellman, Tetrahedron 55, 8883 (1999)
79. R.A. Olofson, J.T. Martz, J.-P. Senet, M. Piteau, T. Malfroot, J. Org. Chem. 49, 2081 (1984)
80. T. Vidal, E. Magnier, Y. Langlois, Tetrahedron 54, 5959 (1998)
81. M.-J. Chen, Y.-M. Tsai, Tetrahedron 67, 1564 (2011)