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Total Syntheses of the Tylophora Alkaloids Cryptopleurine, (−)-Antofine, (−)-Tylophorine, and (−)-Ficuseptine C

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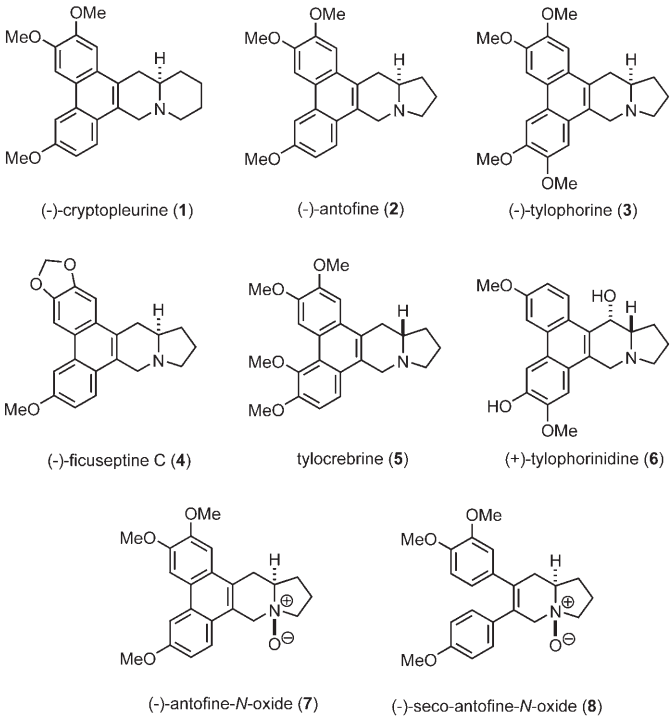
Abstract: A concise, efficient and modular approach to the tylophora alkaloids is described, a family of potent cytotoxic agents that are equally effective against drug sensitive and multidrug resistant cancer cell lines. The advantages of the chosen route are illustrated by the total syntheses of the phenanthroquinolizidine cryptopleurine (**1**) and the phenanthroindolizidines (−)-antofine (**2**), (−)-tylophorine (**3**), and their only recently isolated congener (−)-ficuseptine C (**4**). The key steps consist in a Suzuki cross-coupling between a (commercial) boronic acid and a simple aryl-1,2-dihalide followed by elaboration of the resulting products into the corresponding 2-alkynyl-biphenyl derivatives **27**, **33**, **41** and **46**. The latter undergo $PtCl_2$-catalyzed cycloisomerizations with formation of the functionalized phenanthrenes **28**, **34**, **42** and **47**, which were transformed into the targeted alkaloids by a deprotection/Pictet–Spengler annulation tandem. Due to the flexibility and robust character of this approach, it might enable a systematic exploration of the pharmacological profile of this promising class of bioactive natural products.

Keywords: alkaloids · anti-cancer agents · cross-coupling · phenanthrenes · platinum

Introduction

Since the first isolation of tylophorine in 1935 from the perennial climbing plant *Tylophora indica* (previously *T. asthmatica*) native to the plains, hills and forests of southern and eastern India,[1] the class of "tylophora alkaloids" produced by various plants of the *Asclepiadaceae* family has grown considerably,[2] presently encompassing close to 100 structurally related phenanthroindolizidines and phenanthroquinolizidines together with their *seco*-derivatives and *N*-oxides.[3] As can be seen from the representative examples depicted in Scheme 1, the defining feature of these pentacyclic natural products is the presence of a highly oxygenated phenanthrene ring fused to a saturated N-heterocycle.

The main interest in alkaloids of this type lies in their diverse and potent pharmacological and medicinal properties.[4] The producing plant *T. indica* has been used for centuries in Ayurvedic medicine for the treatment of various ailments of the respiratory tract such as allergies and asthma. Current research supports this traditional use, finding that tylophora extracts may have health benefits including anti-inflammatory, antihistaminic, antiasthmatic, and immunomodulatory effects.[4]



Scheme 1. Representative tylophora alkaloids.

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Most promising, however, are the remarkable cytotoxic activities of many compounds of this series.[2,5,6] Prototype members such as antofine (**2**) are not only distinguished by IC_{50} values in the low nanomolar range, but were also found to be equally effective against drug-sensitive as well as multidrug-resistant (MDR) human cancer cell lines.[6] This remarkable profile suggests that phenanthroindolizidines might be poor substrates for the glycoprotein efflux pump responsible for the MDR phenotype, thus emphasizing a potential role as therapeutic leads in the quest for more effective anti-cancer agents.

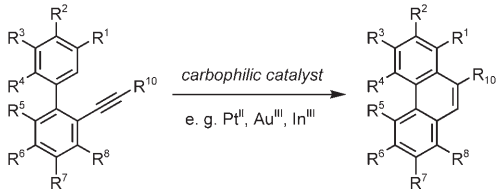
Unfortunately, early clinical trials with tylocrebrine (**5**) had to be stopped due to serious side effects on the central nervous system manifested as ataxia and disorientation.[7] However, it was recently suggested that the use of more polar analogues might allow one to uncouple cyto- and CNS-toxicity, as such derivatives should be less prone to pass the blood/brain barrier; moreover, tissue specific drug delivery techniques can also be envisaged.[6] Therefore it seems appropriate to re-investigate this class of alkaloids both from the medicinal as well as chemical point of view. To this end, a synthetic route is desirable that allows for an efficient fusion of their conserved pyrrolidine- or piperidine parts[8] with a large variety of backbone architectures of different polarity by chemically robust and reliable transformations; ideally, such an approach should be amenable to combinatorial techniques. Although the tylophora alkaloids served as prominent targets in the past,[3] the described approaches, though elegant and creative, do not fully meet modern standards in terms of the desirable structural modularity. Most notably, systematic variations of the oxygenation pattern of the phenanthrene entity are difficult to achieve by many of the established routes.

As part of our investigations into the synthesis[9] and evaluation[10] of bioactive natural products of different origin and structure, we set out to develop an access route to the tylophora alkaloids that is both efficient and flexible. As will be outlined below, recourse to modern cross-coupling techniques and metal catalyzed cycloisomerization reactions allows for the preparation of a set of representative members of this family from simple and, in part, even commercial building blocks. Since alterations of the required components are trivial while maintaining a conserved synthesis blueprint, this methodology might enable optimization of the pharmacological profiles of these potent cytotoxic agents by more systematic modifications of their basic skeletons.

Results and Discussion

Strategic considerations and exploratory studies: Recent investigations from this laboratory have shown that exposure of biaryl derivatives bearing an alkyne unit on one of their *ortho*-positions to catalytic amounts of carbophilic Lewis acids such as $PtCl_2$, AuCl, $AuCl_3$, or $InCl_3$ engenders an efficient cycloisomerization with formation of polycyclic (hetero)arenes.[11]

This method tolerates many functional groups and is particularly well suited for the preparation of phenanthrenes and heterocyclic analogues thereof (Scheme 2).[11] Since the required biphenyl substrates are readily available, for example, by standard cross-coupling techniques, this method opens access to a host of product structures and has already borne scrutiny in the realm of natural product synthesis.[11,12]

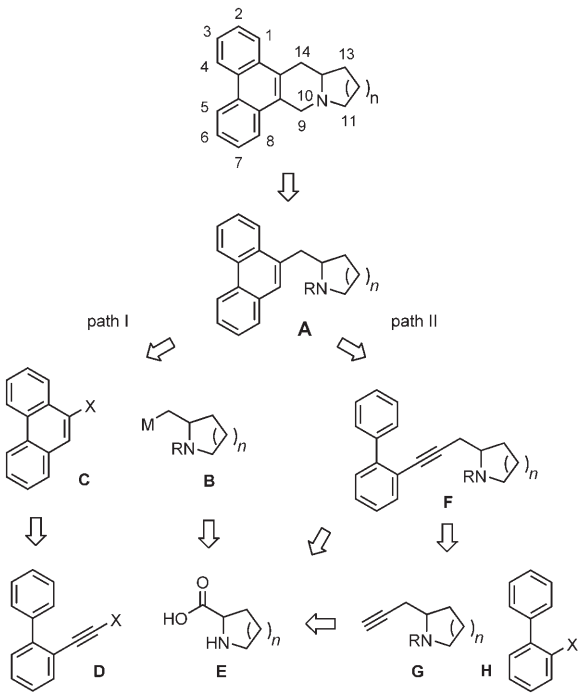


Scheme 2. Formation of (functionalized) polycyclic arenes by metal-catalyzed cycloisomerization. This method is equally applicable to the preparation of condensed heteroaromatic skeletons if the phenyl rings in the substrate are replaced by heteroarene moieties.

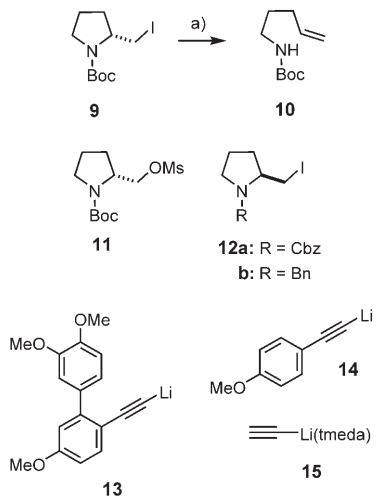
In the present context, this transformation allows deconvolution of the target alkaloids into simple building blocks as shown in Scheme 3. After a Pictet–Spengler transform encoding the final annulation,[13] retrosynthetic cleavage at the C14/C14a bond dissects the key intermediate **A** into a suitably protected aminoalcohol derivative **B** and a 10-halophenanthrene **C** (X = halogen) which derives from a haloalkyne of type **D** by the metal-catalyzed cycloisomerization referred to above. Alternatively, the heterocycle might already be in place during the formation of the phenanthrene backbone by cycloisomerization of alkyne **F**, which in turn should be accessible by cross-coupling between precursors of type **G** and **H**, or **B** (or **E**)and **D** (X = H), respectively.

Although this analysis promises a considerable degree of flexibility, several conceivable routes were dismissed during our exploratory studies. Specifically, we were unable to convert the proline-derived iodide **9** into an organometallic reagent suitable for cross-coupling with a halophenanthrene of type **C** (Scheme 4). Although β-aminosubstituted organozinc reagents are well known in the literature and have been successfully employed in Negishi cross-coupling reactions,[14,15] attempted insertion of activated zinc dust into **9** led only to reductive ring opening with formation of **10**.[16] Likewise, several attempts to form compounds of type **F** by alkylation of the acetylenic nucleophiles **13**–**15** with one of the prolinol derivatives **9**, **11** or **12** under various conditions essentially met with failure.

Therefore we focused our efforts on the assembly route envisaging cross-coupling of a biphenyl **H** with an alkyne **G** carrying the intact pyrrolidine ($n=1$) or piperidine ring ($n=2$) to be incorporated into the final target. Gratifyingly, this sequence proved to be effective as evident from the total syntheses of cryptopleurine (**1**), (−)-antofine (**2**), (−)-tylophorine (**3**), and their only recently discovered congener (−)-ficuseptine C (**4**) that are outlined below.



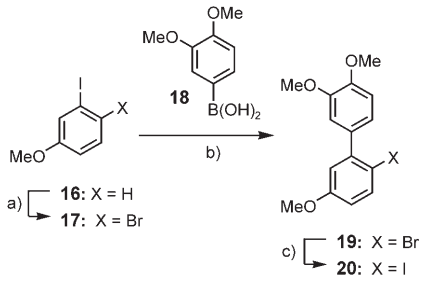
Scheme 3. Retrosynthetic analysis of phenanthroindolizidine- ($n=1$) and phenanthroquinolizidine ($n=2$) alkaloids.



Scheme 4. a) Zn dust (activated with 1,2-dibromoethane and TMSCl), DMF.

Cryptopleurin: Isolated as early as 1948 from the bark of the Australian laurel *Cryptocarya pleurosperma*,[17] cryptopleurine (**1**) constitutes the parent compound of the phenanthroquinolizidine alkaloid family. **1** acts as a potent inhibitor of protein biosynthesis and shows pronounced cytotoxicity in the standard assays.[3,4] This particular alkaloid and several structural variants thereof were later also found in a variety of other plants belonging to the *Lauraceae*, *Vitidaceae* and *Urticaceae* genera and served as prominent target for many total syntheses campaigns in the past.[3,18]

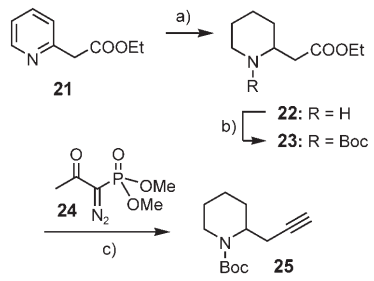
In order to be competitive, any new synthesis of **1** must therefore not only be highly productive but should also be more flexible by design than its ancestors. To this end (Scheme 5), compound **16** was brominated on a large scale to give dihalide **17** as a single isomer in virtually quantitative yield. As expected, this compound underwent a selective Suzuki coupling[19] with the commercial boronic acid **18** at the more reactive C–I bond, which was best performed under conditions previously optimized in this laboratory for similar purposes.[20] The resulting bromide **19**, however, turned out to be insufficiently reactive for the envisaged Sonogashira-type coupling[21] (see below) and had to be transformed into iodide **20** via lithiation followed by quench with elemental iodine. An aromatic Finkelstein reaction as recently described by Buchwald et al.[22] is also able to bring about this transformation in satisfactory yield, but the reaction time was found to be impractically long.



Scheme 5. a) Br_2, HOAc, 99%; b) [(dppf)$PdCl_2$] (5 mol%), LiCl, Na_2CO_3, DME/H_2O, 70%; c) *n*-BuLi, THF, −78°C, then I_2, 1 h, 82%; or: NaI, CuI, dimethylethylene diamine, 1,4-dioxane, 115°C, 7 d, 75%.

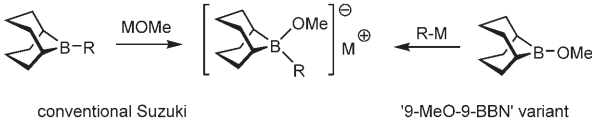
The preparation of the required coupling partner **25** started with the hydrogenation of pyridylacetate **21** over PtO_2 as the precatalyst,[23] followed by Boc protection of the resulting piperidine **22** to give the β-aminoester derivative **23** (Scheme 6). A very effective one-pot, two-step sequence[24] then converted this material to the required alkyne **25** by initial Dibal-H reduction followed by treatment of the corresponding aldehyde with the Ohira–Bestmann reagent **24**.[25,26]

The next step in the assembly process was the coupling of the two fragments in hand via a Sonogashira-type reac-



Scheme 6. a) PtO_2 (3 mol%), H_2 (1 atm), EtOH, HCl, 79%; b) Boc_2O, Et_3N, CH_2Cl_2, 94%; c) i) Dibal-H, CH_2Cl_2, −78°C; ii) compound **24**, K_2CO_3, MeOH, 0°C → RT, 75%.

tion.[21] In the present case, however, this seemingly routine transformation was very low yielding under a variety of experimental conditions and mainly led to competitive homodimerization of alkyne **25**. Gratifyingly though, recourse to the "9-MeO-9-BBN variant" of the Suzuki reaction previously developed in this laboratory[27,28] opened a convenient and high yielding access to the desired product **27**. Rather than generating the required borate nucleophile by reaction of an organoborane substrate with a suitable base, the reactive intermediate is formed from 9-MeO-9-BBN on treatment with an organolithium or other polar organometallic reagent R-M (Scheme 7). If the latter is an alkynylmetal species, the resulting borate complex readily transfers its alkynyl substituent to aryl halides or triflates under palladium catalysis.[27]



Scheme 7. Preparation of the borate donor necessary for Suzuki cross-coupling reactions either via the conventional route or by the "9-MeO-9-BBN" variant.

This methodology was easily implemented as shown in Scheme 8. Thus, deprotonation of **25** with *n*-BuLi in THF at −40 °C gave an alkynyllithium reagent that was trapped with 9-MeO-9-BBN to give borate **26**, which then reacted smoothly with iodide **20** in the presence of [(dppf)$PdCl_2$] (5 mol %) to give product **27** in 82 % yield. Exposure of this compound to catalytic amounts of $PtCl_2$ in toluene at 60 °C engendered a cycloisomerization[11] with formation of phenanthrene **28** which could be isolated in almost quantitative yield. In this transformation, the chosen dilution was found to be key to success: while all reactions performed at $c =$ 0.05 M gave excellent and well reproducible results, attempted cycloisomerizations in 0.2 M solution were much lower yielding (35–50 %), most likely due to competing oligomerizations of the substrate. The constitution of phenanthrene **28** as the key intermediate of this route to crytopleurine could be confirmed by X-ray structure analysis (Figure 1).

The total synthesis then ended with a one-pot tandem deprotection/cyclization process, converting compound **28** into cryptopleurine (**1**) in 67 % yield. In this sequence, the deprotection step occurred rapidly, while the Pictet–Spengler cyclization[13] turned out to be rate determining. Although this latter transformation followed previous procedures, slight modifications in the work-up had a beneficial effect on the yield and purity of the final product (cf. Experimental Section).

In summary, cryptopleurine (**1**) as a prototype phenanthroquinolizidine alkaloid was prepared from three cheap and commercial starting materials by a high yielding and scalable route comprising only six steps in the longest linear sequence. The modular character of this approach will become evident from its ready adaptation to the total syntheses of three related phenanthroindolizidine derivatives. Although this exploratory study afforded racemic **1**, it can be adapted to the preparation of optically active cryptopleurine as well;[26] all three companion syntheses described below bear witness for this notion. Moreover, (±)-**1** can be easily resolved by chiral HPLC.

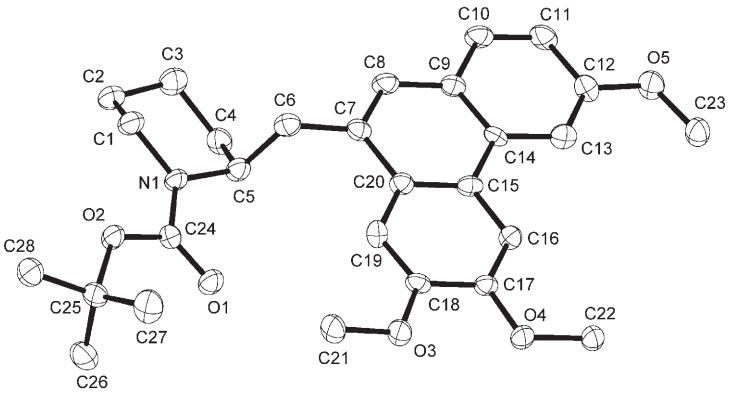
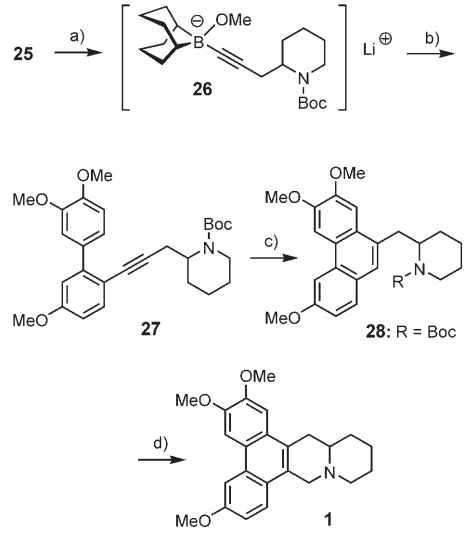


Figure 1. Molecular structure of phenanthrene **28** from single crystal X-ray structure determination. Anisotropic displacement ellipsoids are shown at the 50 % probability level and hydrogen atoms have been omitted for clarity.

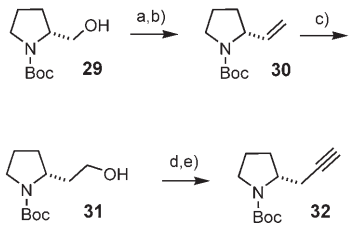


Scheme 8. a) *n*-BuLi, THF, −40 °C, then 9-MeO-9-BBN, RT; b) iodide **20**, [(dppf)$PdCl_2$] (5 mol %), THF, reflux, 82 %; c) $PtCl_2$ (20 mol %), toluene (0.05 M), 60 °C, 3 h, 97 %; d) aq. HCHO, HCl/EtOH, 80 °C, 67 %.

(−)-Antofine: Since cryptopleurine (**1**) and antofine (**2**) share a common phenanthrene skeleton, it was obvious to divert the route leading to **1** to the preparation of this latter target.[29] Antofine is known as an exceptionally potent cytotoxic agent that is active against human drug sensitive and multidrug resistant cancer cell lines alike.[3–6] For its synthesis, it sufficed to replace alkyne **25** bearing a piperidine ring

by the formally ring contracted analogue **32**, for which an effective preparation had to be developed.

As already mentioned above, attempts to obtain this compound by alkynylation of prolinol derivatives **9**, **11** or **12** were unrewarding (Scheme 4). Therefore, an alternative route starting from a homoproline derivative as the substrate was pursued that is summarized in Scheme 9. Al-

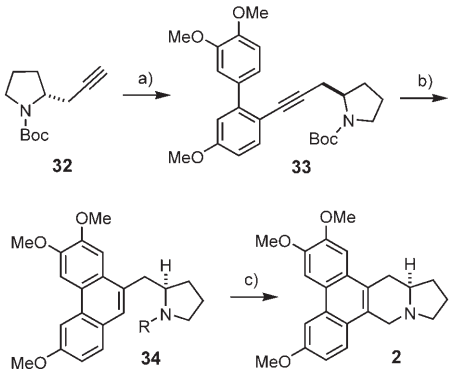


Scheme 9. a) 'Tetra-*n*-propylammonium perruthenate (TPAP) (5 mol%), *N*-morpholine-*N*-oxide (NMO), CH_2Cl_2, 82%; b) $Ph_3P{=}CH_2$, THF, 61%; c) i) 9-BBN, THF; ii) $NaBO_3{\cdot}4H_2O$, H_2O, 88%; d) TPAP (5 mol%), NMO, CH_2Cl_2, 73%; e) Bestmann–Ohira reagent **24**, K_2CO_3, MeOH, 55% (*ee* > 99.5, chiral GC).

though homoproline itself is commercially available, this particular β-amino acid is rather expensive and only offered as the undesired *S* isomer. Likewise, several literature procedures for the one-carbon homologation of proline to homoproline were dismissed for practicality reasons and/or because they were plagued by impractically low yields.[30]

The slightly longer but robust alternative depicted in Scheme 9, however, reliably provided the required alkyne **32** in optically pure form (*ee* > 99.5%).[31] Specifically, oxidation of *N*-Boc-prolinol **29**[32] with the tetra-*n*-propylammonium perruthenate (TPAP) cat./*N*-methylmorpholine-*N*-oxide (NMO) couple[33] followed by Wittig olefination of the resulting aldehyde furnished alkene **30** which was subjected to hydroboration/oxidation to give alcohol **31**. TPAP oxidation of this alcohol and reaction of the resulting aldehyde with the Ohira/Bestmann reagent **24**[25] delivered the desired alkyne **32** in good overall yield.[34]

With building block **32** in optically active form in hand, the preparation of (−)-antofine (**2**) could be easily completed (Scheme 10). Thus, 9-MeO-9-BBN mediated cross-coupling[27] of **32** with iodide **20** already used in the cryptopleurine series followed by platinum-catalyzed rearrangement[11] of the resulting alkynylated biphenyl derivative **33** furnished the desired phenanthrene **34**. Cleavage of the Boc group followed by Pictet–Spengler cyclization[13] could again be performed as a one-pot operation which furnished antofine (**2**) in high yield. Not only did the analytical and spectroscopic data of our samples match those of the natural product reported in the literature,[29] but the synthetic material was also found to be optically pure within the limits of detection (> 98%, HPLC). This result shows that pre-existing chiral centers are not compromised in any step of the chosen sequence.

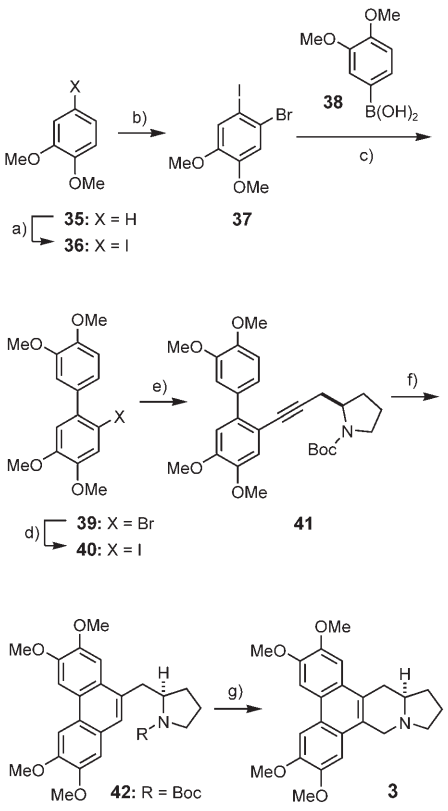


Scheme 10. a) i) *n*-BuLi, THF, −40°C, then 9-MeO-9-BBN, RT; ii) iodide **20**, [(dppf)$PdCl_2$] (5 mol%), THF, reflux, 58%; b) $PtCl_2$ (20 mol%), toluene (0.01 M), 60–80°C, 3 h, 72%; c) aq. HCHO, HCl/EtOH, 80°C, 91% (*ee* > 98%, chiral HPLC).

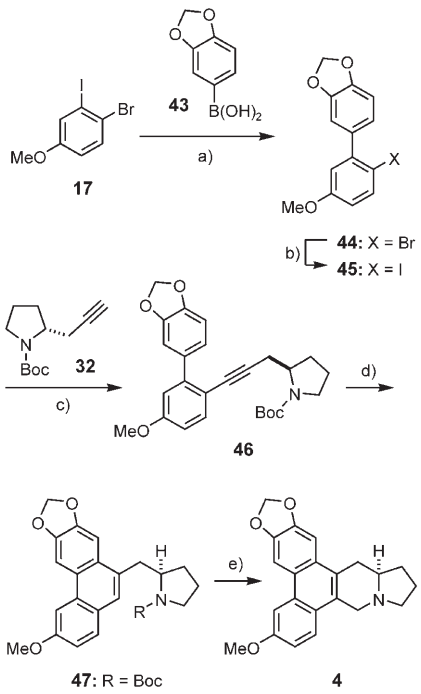
(−)-Tylophorine: The preparation of (−)-tylophorine (**3**) as the parent compound of the phenanthroindolizidine series[1,35] used the same pyrrolidine building block **32** as our synthesis of (−)-antofine but required a more highly oxygenated biphenyl derivative as the coupling partner.

This building block was prepared by regioselective iodination of veratrole **35**[36] followed by bromination of the resulting product **36** under standard conditions (Scheme 11). Although this compound contained some dibromide contaminant that could not be separated at this stage, it was amenable to a subsequent Suzuki reaction with the commercial boronic acid **38** under the previously optimized conditions[11,20] to give analytically pure biaryl **39**. Iodine for bromine exchange (**39** → **40**) followed by a second Suzuki cross-coupling, now via the 9-MeO-9-BBN variant,[27] allowed for attachment of the alkyne entity, which set the stage for the platinum-catalyzed cylcoisomerization[11] of **41** with formation of the functionalized phenanthrene **42**. This key intermediate was then converted into (−)-tylophorine (**3**) by the established deprotection/cyclization tandem. As in the previous cases, the spectral characteristics as well as the optical rotation of the synthetic sample were in excellent agreement with the literature data.[13c]

(−)-Ficuseptine C: The leaves of the subtropic tree *Ficus septica* Burm. f. (*Moraceae*), which grows abundantly in Taiwan, are widely used in traditional Chinese medicine for their purgative and emetic effects to treat colds, fevers and infective diseases. A recent search for the bioactive components showed that the methanol extract also exhibits potent cytotoxic properties due to the presence of a cocktail of various phenanthroindolizidine alkaloids.[37] In addition to several known members of this series (including tylophorine (**3**), tylocrebrine (**5**) and antofine-*N*-oxide (**7**)), 8 new alkaloids of this type have been isolated and characterized; unfortunately, however, some of them were obtained in minute amounts only, thus making a detailed assessment of their biological properties impossible; (−)-ficuseptine C (**4**) belongs to this group (only 1 mg of product was isolated from



Scheme 11. a) I_2, HgO, CH_2Cl_2, 97%; b) Br_2, HOAc, 67%; c) boronic acid **38**, [(dppf)$PdCl_2$] (5 mol%), LiCl, Na_2CO_3, DME/H_2O, 80°C, 59%; d) *n*-BuLi, THF, −78°C, then I_2, −78°C → RT, 54%; e) i) alkyne **32**, *n*-BuLi, THF, −40°C, ii) 9-MeO-9-BBN, RT; iii) iodide **40**, [(dppf)$PdCl_2$] (5 mol%), THF, reflux, 64%; f) $PtCl_2$ (20 mol%), toluene (0.05 M), 60–80°C, 56%; g) aq. HCHO, HCl/EtOH, 80°C, 48% (*ee* > 98%, chiral HPLC).



Scheme 12. a) Boronic acid **43**, [(dppf)$PdCl_2$] (5 mol%), LiCl, Na_2CO_3, DME/H_2O, 80°C, 41%; b) *n*-BuLi, THF, −78°C, then I_2, −78°C → RT, 77%; c) i) alkyne **32**, *n*-BuLi, THF, −40°C, ii) 9-MeO-9-BBN, RT; iii) iodide **45**, [(dppf)$PdCl_2$] (5 mol%), THF, reflux, 59%; d) $PtCl_2$ (20 mol%), toluene (0.05 M), 60–80°C, 56%; e) aq. HCHO, HCl/EtOH, 80°C, 62% (*ee* > 98%, chiral HPLC).

46.5 kg of plant material).[37] Due to the close structural relationship with the other alkaloids discussed herein, we set out to prepare meaningful quantities of this compound in order to confirm its structure and to enable a preliminary biochemical and biological profiling.

In view of the flexibility of our assembly process, this goal was easily attained as summarized in Scheme 12. Thus, it sufficed to engage boronic acid **43** in the Suzuki reaction with iodide **17** to give biphenyl **44** in an unoptimized 41% yield. Metal–halogen exchange followed by addition of I_2 afforded iodide **45** ready for cross-coupling with alkyne **32** via the 9-MeO-9-BBN-based methodology described above.[27] Subsequent cycloisomerization of the resulting product **46** with the aid of $PtCl_2$ in toluene[11] gave the somewhat labile phenanthrene **47** which was converted into the targeted alkaloid **4** by the usual deprotection/cyclization protocol.

Synthetic (−)-ficuseptine C was a beige solid rather than a colorless gum as described in the literature;[37] moreover, its specific optical rotation deviated significantly from that of the isolated natural product (cf. Experimental Section). Worried about these discrepancies, a very detailed spectroscopic analysis of the compound was carried out which unambiguously proved the proposed constitution as well as purity and integrity of our synthetic material. The original spectra of **4**, kindly provided by Professor Wu (Taiwan), matched our spectra; however, they also suggested that contaminants from the extraction process had remained in the original sample which might explain the differences in appearance and $[\alpha]_D$. We therefore believe that the analytical and spectroscopic data recorded for synthetic (−)-**4**, as compiled in the Experimental Section, represent the correct reference data set for (−)-ficuseptine C. Biochemical evaluations of this compound and its congeners will be disclosed in due course.

Conclusion

This report describes the establishment of a concise, efficient and modular synthetic route to typlophora alkaloids. The versatility and flexibility of the method was demonstrated by the preparation of four representative members belonging to the phenanthroquinolizidine as well as the phenanthroindolizidine series. These examples illustrate that modification of the substitution pattern around the phenanthrene ring as well as of the heterocyclic segments are easily accommodated due to the flexibility inherent to the underlying synthesis blueprint. Key transformations include palladium catalyzed cross-coupling reactions for the formation of the biphenyl scaffold as well as for the introduction of the

alkynyl substituent at one of the *ortho*-positions. The reliability of these methods and the ready availability of a host of suitable building blocks suggest that systematic explorations of pertinent structure/activity relationships as well as a fine tuning of the physico-chemical properties of the resulting products should be fairly straightforward. This modular character might enable an optimization of the pharmacological profile of these highly cytotoxic alkaloids. Moreover, the success of this total synthesis campaign also attests to the maturity of the $PtCl_2$-catalyzed cycloisomerization reaction leading to substituted phenanthrene derivatives and (heterocyclic) analogues thereof.[11,12] Further applications of this and related methodologies to natural product synthesis together with a first round of biological evaluations is presently ongoing and will be reported in the near future.

Experimental Section

General methods: All reactions were carried out under Ar in flame-dried glassware. The solvents used were purified by distillation over the drying agents indicated and were transferred under Ar: THF, Et_2O, DME (Mg/anthracene), CH_2Cl_2, 1,2-dichloroethane (P_4O_{10}), MeCN, Et_3N, NMP (CaH_2), MeOH, *i*PrOH (Mg), hexane, benzene, toluene (Na/K). Flash chromatography: Merck silica gel 60 (230–400 mesh); where indicated, flash chromatography was performed with the aid of a Combiflash Companion apparatus using pre-packed RediSep columns. NMR: Spectra were recorded on a Bruker DPX 300 or AV 400 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: $\delta_C \equiv$ 77.0 ppm; residual $CHCl_3$ in $CDCl_3$: $\delta_H \equiv$ 7.24 ppm; CD_2Cl_2: $\delta_C \equiv$ 53.8 ppm; residual CH_2Cl_2 in CD_2Cl_2: $\delta_H \equiv$ 5.32 ppm). Where indicated, the signal assignments are unambiguous; the numbering scheme is arbitrary and is shown in the inserts. The assignments are based upon 1D and 2D spectra recorded using the following pulse sequences from the Bruker standard pulse program library: DEPT; COSY (cosygs and cosydqtp); HSQC (invietgssi) optimized for $^1J(C,H) = 145$ Hz; HMBC (inv4gslplrnd) for correlations via $^nJ(C,H)$; HSQC-TOCSY (invietgsml) using an MLEV17 mixing time of 120 ms. IR: Nicolet FT-7199 spectrometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: Finnigan MAT 95, accurate mass determinations: Bruker APEX III FT-MS (7 T magnet). Melting points: Büchi melting point apparatus B-540 (corrected). Elemental analyses: H. Kolbe, Mülheim/Ruhr. Unless stated otherwise, all commercially available compounds (Fluka, Lancaster, Aldrich) were used as received.

Cryptopleurine series

3-Iodo-4-bromoanisole (17): Br_2 (2.8 mL, 54 mmol) was added dropwise to a solution of 3-iodoanisole (**16**; 10.01 g, 42.79 mmol) in glacial HOAc (65 mL) and the resulting orange mixture was stirred at ambient temperature for 26 h. For work up, the solution was diluted with water (250 mL) and extracted with hexanes (5×50 mL). The combined orange extracts were washed with aq. $Na_2S_2O_3$ (5%, 3×25 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated to an orange oil (13.32 g). Kugelrohr distillation (250 °C, 0.1 Torr) gave product **17** as a pale brown oil (13.24 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.46$ (d, $J = 8.8$ Hz, 1H), 7.38 (d, $J = 2.8$ Hz, 1H), 6.76 (dd, $J = 8.8$ Hz, 2.8 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 158.8$, 132.6, 125.5, 120.3, 116.0, 101.1, 55.7; IR (film): $\tilde{\nu} = 3082$, 2934, 1580, 1460, 1284, 1228, 1034, 833, 802, 602 cm^{-1}; MS (EI): m/z (%): 314 (98) [$M(^{81}Br)^+$], 312 (100) [$M(^{79}Br)^+$], 299 (9), 297 (9), 271 (8), 269 (8), 172 (17), 170 (17), 63 (42); HRMS (EI): m/z: calcd for $C_7H_6I^{79}BrO$: 311.864688; found: 311.864329 [M^+].

2-Bromo-3′,4′,5-trimethoxybiphenyl (19): A mixture of aryl iodide **17** (1.94 g, 6.20 mmol), boronic acid **18** (1.22 g, 6.70 mmol), LiCl (0.92 g, 22 mmol), degassed aq. Na_2CO_3 (2 M, 17 mL, 34 mmol), and [(dppf)$PdCl_2$] (234 mg, 0.287 mmol) in DME (50 mL) was stirred at 80 °C for 21 h. The mixture was cooled to ambient temperature, diluted with aq. NH_4Cl (50 mL) and extracted with *tert*-butyl methyl ether (4×25 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. Evaporation of the solvents afforded the crude product as a dark oil which was purified by flash chromatography (20% *tert*-butyl methyl ether in hexanes) to give biaryl **19** as a colorless oil which slowly solidified over time (1.40 g, 70%). M.p. 56–58 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.53$ (d, $J = 8.8$ Hz, 1H), 7.01–6.90 (m, 3H), 6.89 (d, $J = 3.1$ Hz, 1H), 6.76 (dd, $J = 8.8$, 3.1 Hz, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 158.9$, 148.7, 148.4, 143.2, 133.9, 133.7, 121.6, 116.9, 114.4, 113.3, 113.0, 110.8, 56.0, 55.9, 55.6; IR (film): $\tilde{\nu} = 3068$, 2935, 1604, 1255, 1028, 808 cm^{-1}; MS (EI): m/z (%): 324 (100) [$M(^{81}Br)^+$], 322 (100) [$M(^{79}Br)^+$], 309 (13), 307 (14), 281 (14), 279 (14), 200 (45); HRMS (EI): m/z: calcd for $C_{15}H_{15}{}^{79}BrO_3$: 322.020470; found: 322.020279 [M^+]; elemental analysis calcd (%) for $C_{15}H_{15}BrO_3$: C 55.75, H 4.68; found: C 55.86, H 4.61.

2-Iodo-3′,4′,5-trimethoxybiphenyl (20): A solution of bromide **19** (249 mg, 0.770 mmol) in THF (1 mL) at −78 °C was treated slowly with *n*-BuLi (1.64 M in hexanes, 0.50 mL, 0.82 mmol). The resulting bright yellow solution was stirred at −78 °C for 5 min and then treated with a solution of I_2 (274 mg, 1.08 mmol) in THF (1 mL). The resulting dark slurry was stirred at −78 °C for 15 min and then at ambient temperature for 1 h. The reaction was quenched with aq. sat. NH_4Cl (5 mL) and enough water to dissolve the resulting precipitate. The layers were separated and the aqueous phase was extracted with *tert*-butyl methyl ether (4×5 mL). The combined organic extracts were washed with 5% aq. $Na_2S_2O_3$ (2×5 mL) and brine (10 mL), before they were dried (Na_2SO_4) and evaporated to a yellow oil (268 mg, 94%) which eventually solidified. This compound was pure enough to use in the subsequent step. The product could be further purified by flash chromatography (1% EtOAc in toluene) to give product **20** as a colorless oil which slowly solidified over time (235 mg, 82%). M.p. 76–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.79$ (d, $J = 8.7$ Hz, 1H), 6.90 (m, 4H), 6.63 (dd, $J = 8.7$, 3.0 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.8$, 148.7, 148.3, 147.3, 140.0, 136.9, 121.5, 116.2, 115.0, 113.0, 110.7, 87.6, 56.0, 55.9, 55.5; IR (film): $\tilde{\nu} = 3054$, 2937, 1603, 1231, 1019, 803 cm^{-1}; MS (EI): m/z (%): 370 (100) [M^+], 355 (7), 327 (6), 243 (2), 200 (8); HRMS (EI): m/z: calcd for $C_{15}H_{15}IO_3$: 370.006592; found: 370.006188; elemental analysis calcd (%) for $C_{15}H_{15}IO_3$: C 48.67, H 4.08; found: C 48.81, H 4.14.

(±)-Ethyl (piperidin-2-yl)acetate (22): A solution of pyridine **21** (1.02 g, 6.14 mmol) in aq. HCl (6 M, 2 mL) and EtOH (10 mL) was treated with PtO_2 (42 mg, 0.19 mmol) and stirred under an atmosphere of H_2 (1 bar) for 20 h. The mixture was filtered through a plug of Celite with EtOH and the filtrate was evaporated. The resulting colorless oil was treated with NH_4OH (14 M, 1.5 mL) and brine (8.5 mL) and extracted with *tert*-butyl methyl ether (5×10 mL). The combined extracts were dried ($MgSO_4$) and evaporated to a colorless oil (832 mg, 79%) which could be further purified by Kugelrohr distillation (200 °C, 0.1 Torr). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.14$ (q, $J = 7.2$ Hz, 2H), 3.04 (m, 1H), 2.91 (dddd, $J = 10.7$, 7.9, 5.5, 2.6 Hz, 1H), 2.66 (m, 1H), 2.36 (m, 1H), 2.34 (d, $J = 2.3$ Hz, 1H), 2.03 (br s, 1H), 1.78 (m, 1H), 1.60 (m, 2H), 1.39 (m, 2H), 1.25 (t, $J = 7.1$ Hz, 3H), 1.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 172.4, 60.4, 53.4, 46.9, 41.8, 32.7, 26.1, 24.7, 14.3; IR (film): $\tilde{\nu} = 3304$, 2932, 1733, 1176 cm^{-1}; MS (EI): m/z (%): 171 (4) [M^+], 142 (6), 84 (100); HRMS (EI): m/z: calcd for $C_9H_{17}NO_2$: 171.125927; found: 171.126149.

(±)-Ethyl (*N*-*tert*-butoxycarbonylpiperidin-2-yl)acetate (23): A solution of piperidine **22** (2.70 g, 15.8 mmol) and NEt_3 (4.5 mL, 32 mmol) in CH_2Cl_2 (25 mL) at 0 °C was treated with Boc_2O (3.40 g, 15.6 mmol) and the resulting mixture was stirred for 18 h. The reaction was successively washed with aq. HCl (1 M, 3×20 mL), aq. sat. $NaHCO_3$ (25 mL) and brine (25 mL), dried (Na_2SO_4) and evaporated, and the residue was purified by Kugelrohr distillation (200 °C, 0.1 Torr) to yield product **23** as a colorless oil (4.02 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$, rotamers): $\delta =$ 4.70 (m, 1H), 4.11 (q, $J = 7.1$ Hz, 2H), 3.99 (m, 1H), 2.78 (m, 1H), 2.55 (m, 2H), 1.7–1.4 (m, 6H), 1.45 (s, 9H), 1.25 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.4$, 154.7, 79.5, 60.4, 48.1, 39.2, 35.4, 28.4, 28.2,

25.3, 18.9, 14.2; IR (film): $\tilde{\nu}$ = 2936, 1737, 1692, 1412, 1392, 1366, 1273, 1161 cm^{-1}; MS (EI): *m/z* (%): 271 (4) [M^+], 215 (5), 170 (40), 128 (45), 84 (100), 57 (57), 41 (14); HRMS: *m/z*: calcd for $C_{14}H_{25}NO_4$+Na: 294.167578; found: 294.167311.

(±)-*N*-*tert*-Butoxycarbonyl-2-propargylpiperidine (25): A solution of compound **23** (2.04 g, 7.52 mmol) in CH_2Cl_2 (15 mL) at −78 °C was treated slowly with Dibal-H (1 M in hexanes, 8.4 mL, 8.4 mmol). After TLC showed that the ester had been consumed (~4 h), the reaction was quenched with MeOH (5 mL) and warmed to 0 °C. This mixture was treated first with a solution of the Bestmann–Ohira reagent **24** (1.45 g, 7.56 mmol) in MeOH (10 mL) and then with K_2CO_3 (2.02 g, 14.6 mmol), stirred for 30 min at 0 °C and then overnight at ambient temperature. After 19 h the yellow slurry was treated with saturated Rochelle salt solution (50 mL) and stirred until all solids had dissolved (~30 min). The aqueous phase was repeatedly extracted with *tert*-butyl methyl ether (6× 15 mL), the combined extracts were washed with brine (50 mL), dried (Na_2SO_4) and evaporated to a yellow oil. Flash chromatography of this residue (10% *tert*-butyl methyl ether in hexanes) gave product **25** as a white solid (1.27 g, 75%). M.p. 52–54 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.41 (m, 1H), 3.99 (m, 1H), 2.73 (m, 1H), 2.44 (m, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.86 (m, 1H), 1.60–1.41 (m, 5H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9, 81.6, 79.5, 69.9, 49.6, 39.1, 28.5, 26.8, 25.2, 19.6, 18.7; IR (film): $\tilde{\nu}$ = 3248, 2942, 1680, 1157 cm^{-1}; MS (EI): *m/z* (%): 223 (1) [M^+], 184 (15), 128 (100), 84 (88), 57 (68); HRMS: *m/z*: calcd for $C_{13}H_{21}NO_2$+Na: 246.146444; found: 246.146246; elemental analysis calcd (%) for $C_{13}H_{21}NO_2$: C 69.92, H 9.48; found: C 69.92, H 9.44.

Representative procedure for cross-coupling via the 9-MeO-9-BBN variant of the Suzuki reaction: **(±)-*N*-*tert*-butoxycarbonyl-2-[3-(3′,4′,5-trimethoxybiphenyl-2-yl)-prop-2-ynyl]piperidine (27)**: A solution of alkyne **25** (42 mg, 0.19 mmol) in THF (1.6 mL) at −40 °C was treated with *n*-BuLi (1.69 M in hexanes, 110 μL, 0.186 mmol) and stirred for 40 min. To this solution was added 9-MeO-9-BBN (37 mg, 0.24 mmol) and the resulting solution was stirred at ambient temperature for 1 h. Iodide **20** (49 mg, 0.13 mmol) and [(dppf)$PdCl_2$] (6 mg, 0.007 mmol) were then added, and the resulting dark mixture was stirred at 80 °C for 21 h. The mixture was cooled to ambient temperature before it was diluted with aq. sat. NH_4Cl (5 mL) and extracted with *tert*-butyl methyl ether (4×5 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, and evaporated to give the crude product as an orange oil which was purified by flash chromatography (Combiflash Companion, 0→30% *tert*-butyl methyl ether in hexanes) to give product **27** as a colorless oil (50 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 8.5 Hz, 1H), 7.13 (m, 1H), 7.11 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.87 (d, *J* = 2.6 Hz, 1H), 6.79 (dd, *J* = 8.6, 2.7 Hz, 1H), 4.32 (br s, 1H), 3.96 (m, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.83 (s, 3H), 2.69 (m, 1H), 2.61 (ABX, J_{AB} = 16.5 Hz, 1H), 2.44 (ABX, J_{AB} = 16.5 Hz, 1H); 1.70–1.22 (m, 6H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 154.9, 148.6, 148.4, 145.0, 134.6, 133.6, 121.6, 114.8, 114.5, 112.8, 112.5, 110.8, 88.4, 81.6, 79.4, 56.0, 55.99, 55.4, 49.9, 39.2, 28.5, 26.6, 25.2, 20.7, 18.7; IR (film): $\tilde{\nu}$ = 2933, 1685, 1602, 1407, 1364, 1251, 1160, 1028, 810 cm^{-1}; MS (EI): *m/z* (%): 465 (7) [M^+], 281 (6), 184 (24), 128 (100), 84 (43), 57 (20); HRMS: *m/z*: calcd for $C_{28}H_{35}NO_5$+Na: 488.240743; found: 488.240514; elemental analysis calcd (%) for $C_{28}H_{35}NO_5$: C 72.23, H 7.58, N 3.01; found: C 72.30, H 7.48, N 2.94.

Representative procedure for the $PtCl_2$-catalyzed cycloisomerization reaction: **Preparation of (±)-*N*-*tert*-butoxycarbonyl-2-[(2,3,6-trimethoxyphenanthren-10-yl)methyl]-piperidine (28)**: A solution of compound **27** (48 mg, 0.10 mmol) in toluene (2 mL) was treated with $PtCl_2$ (5 mg, 0.02 mmol) and stirred at 60 °C for 3 h. The mixture was adsorbed on silica gel and the product was purified by flash chromatography (Combiflash Companion, 0→25% *tert*-butyl methyl ether in hexanes) to give phenanthrene **28** as a white powder (47 mg, 97%). The enantiomers can be separated by chiral HPLC (Chiralpak AD-H (250 mm×4.6 mm), *n*-heptane/isopropanol 4:1, 0.5 mL min^{-1}, 14.90 min, 20.29 min). M.p. 190–191 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (s, 1H), 7.85–7.75 (br s, 1H), 7.84 (d, *J* = 2.3 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.37 (s, 1H), 7.16 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.69 (m, 1H), 4.15 (br s, 3H), 4.11 (s, 3H), 4.06 (m, 1H), 4.00 (s, 3H), 3.23 (m, 2H), 3.08 (dt, *J* = 13.2, 2.9 Hz, 1H), 1.90–1.61 (m, 4H), 1.52–1.40 (m, 2H), 1.26 (br s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 155.1, 149.7, 148.8, 130.6, 130.5, 129.6, 127.2, 126.0, 125.8, 124.8, 115.3, 105.8, 103.9, 79.0, 56.4, 56.1, 55.6, 50.2, 39.6, 34.0, 29.7, 28.2, 25.6, 18.9; IR (film): $\tilde{\nu}$ = 2937, 1673, 1620, 1607, 1413, 1363, 1160, 1030, 835 cm^{-1}; MS (EI): *m/z* (%): 465 (18) [M^+], 282 (21), 281 (39), 184 (18), 128 (100), 84 (34), 57 (14); HRMS: *m/z*: calcd for $C_{28}H_{35}NO_5$+Na: 488.240742; found: 488.240956; elemental analysis calcd (%) for $C_{28}H_{35}NO_5$: C 72.23, H 7.58, N 3.01; found: C 72.25, H 7.67, N 2.89.

Representative procedure for the deprotection/Pictet–Spengler cyclization tandem: **(±)-cryptopleurine (1)**: A solution of phenanthrene **28** (75 mg, 0.16 mmol) in EtOH (5 mL) was treated with aqueous HCHO (37% *w/w*, 1.0 mL, 12 mmol) and HCl (12 M, 0.15 mL, 1.8 mmol), and the resulting mixture was stirred at 80 °C in the dark for 4 d. The solvents were evaporated and the residue was dissolved in NaOH (6 M, 5 mL) and extracted with CH_2Cl_2 (4×5 mL). The combined extracts were successively washed with water (6×5 mL) and brine (5 mL), dried (Na_2SO_4), and evaporated to give a light brown solid which was further purified by flash chromatography (Combiflash Companion, 0→15% EtOH in CH_2Cl_2) to give cryptopleurine (**1**) as a yellow-green powder (41 mg, 67%). The enantiomers can be separated by chiral HPLC (Chiralpak AD-H (250 mm×4.6 mm), *n*-heptane/isopropanol 4:1, 0.5 mL min^{-1}, 42.52 min, 48.27 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (s, 1H), 7.87 (d, *J* = 2.6 Hz, 1H), 7.76 (d, *J* = 9.0 Hz, 1H), 7.22 (s, 1H), 7.18 (dd, *J* = 9.0, 2.6 Hz, 1H), 4.42 (d, *J* = 15.5 Hz, 1H), 4.08 (s, 3H), 4.04 (s, 3H), 4.00 (s, 3H), 3.61 (d, *J* = 15.5 Hz, 1H), 3.26 (d, *J* = 11.0 Hz, 1H), 3.05 (dd, *J* = 16.5, 3.1 Hz, 1H), 2.87 (dd, *J* = 16.0, 10.5 Hz, 1H), 2.38 (m, 1H), 2.29 (m, 1H), 2.02 (dd, *J* = 12.9, 2.5 Hz, 1H), 1.88 (d, *J* = 12.6 Hz, 1H), 1.81 (m, 2H), 1.55 (m, 1H), 1.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.5, 149.5, 148.4, 130.2, 126.5, 125.4, 124.4, 124.1, 123.7, 123.5, 114.9, 104.8, 104.00, 103.96, 57.6, 56.2, 56.05, 55.96, 55.5, 34.6, 33.7, 25.9, 24.3; IR (film): $\tilde{\nu}$ = 2929, 1610, 1256, 1041 cm^{-1}; MS (EI): *m/z* (%): 377 (32) [M^+], 294 (100), 279 (4), 189 (6); HRMS: *m/z*: calcd for $C_{24}H_{28}NO_3$: 378.206370; found: 378.206195.

Antofine series

(*R*)-*N*-(*tert*-Butoxycarbonyl)-2-ethenylpyrrolidine (30):[38] A solution of Boc-prolinol **29** (7.44 g, 36.95 mmol)[32] and NMO (6.57 g, 56.07 mmol) in CH_2Cl_2 (75 mL) was treated with powdered molecular sieves (3 Å, 19.2 g) and then with TPAP (649 mg, 1.85 mmol),[33] resulting in a brief exothermic reaction. The dark mixture was stirred at ambient temperature for 3.5 h and then filtered through a silica gel column with *tert*-butyl methyl ether. Evaporation of the filtrate afforded (*R*)-*N*-(*tert*-butoxycarbonyl)-prolinal as a colorless oil (6.06 g, 82%) which was used without further purification. Characteristic data:[39] ^{1}H NMR (400 MHz, $CDCl_3$, rotamers): δ = 9.56 (m) and 9.46 (d, *J* = 2.9 Hz) (1H), 4.20 and 4.06 (m, 1H), 3.50 (m, 2H), 2.2–1.6 (m, 4H), 1.49 and 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.7, 200.4, 155.0, 154.0, 80.7, 80.2, 65.1, 64.9, 46.9, 46.8, 28.4, 28.3, 28.0, 26.8, 24.7, 24.0; IR (film): $\tilde{\nu}$ = 2977, 1735, 1687, 1389, 1159, 1118 cm^{-1}; MS (EI): *m/z* (%): 170 (14) [M^+−CHO], 126 (12), 114 (50), 70 (94), 57 (100), 41 (23), 29 (15); HRMS: *m/z*: calcd for $C_{10}H_{18}NO_3$: 200.128669; found: 200.128424.

A yellow solution of $Ph_3P{=}CH_2$ (2.28 g, 8.23 mmol) in THF (5 mL) was treated with a solution of the crude prolinal described above (1.51 g, 7.57 mmol) in THF (10 mL). After stirring for 3 h, the reaction mixture was absorbed onto silica gel and purified by flash chromatography (10% *tert*-butyl methyl ether in hexanes) to give compound **30** as a colorless oil (907 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.76 (ddd, *J* = 16.6, 10.6, 5.9 Hz, 1H), 5.05 (m, 2H), 4.30 (m, 1H), 3.39 (m, 2H), 2.01 (m, 1H), 1.84 (m, 2H), 1.69 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 138.9, 113.7, 79.1, 59.1, 46.3, 31.8, 28.5, 23.0; IR (film): $\tilde{\nu}$ = 3083, 2975, 1697, 1643, 1394, 1171, 1114, 988, 914 cm^{-1}; MS (EI): *m/z* (%): 197 (6) [M^+], 141 (56), 124 (15), 70 (17), 57 (100), 41 (29), 29 (13); HRMS: *m/z*: calcd for $C_{11}H_{19}NO_2$+Na 220.130800; found: 220.130884.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-2-(hydroxyethyl)-pyrrolidine (31): The solution of olefin **30** (907 mg, 4.60 mmol) in THF (9 mL) at 0 °C was treated with 9-BBN dimer (866 mg, 3.52 mmol). After 1 h the mixture was allowed to warm to ambient temperature and stirring was continued for 5 h. $Na_2BO_3{\cdot}4H_2O$ (3.22 g, 20.9 mmol) and water (10 mL) were then added, and the resulting mixture was allowed to stir at ambient tempera-

ture for 18 h. For work up, the mixture was diluted with water (75 mL) and extracted with *tert*-butyl methyl ether (5×20 mL). The combined organic layers were washed with brine (25 mL), dried (Na_2SO_4), and evaporated and the residue was purified by flash chromatography (Combiflash Companion, 0→50% *tert*-butyl methyl ether in hexanes) to give product **31** as a colorless oil (868 mg, 88%).[40] ^{1}H NMR (400 MHz, $CDCl_3$, rotamers): δ=4.13 (m, 1H), 3.59 (m, 2H), 3.33 (m, 2H), 2.93 (brs, 1H), 1.97 (m, 1H), 1.88 (m, 2H), 1.65 (m, 2H), 1.50–1.31 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=79.9, 59.3, 53.6, 46.4, 38.4, 31.2, 28.5, 23.5; MS (EI): *m*/*z* (%): 215 (4) [M^+], 170 (14), 142 (11), 114 (86), 70 (100), 57 (100), 41 (29), 29 (17); HRMS: *m*/*z*: calcd for $C_{11}H_{21}NO_3$+Na: 238.141361; found: 238.141392.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-2-propargylpyrrolidine (32): A mixture of homoprolinol **31** (2.62 g, 12.2 mmol), NMO (2.16 g, 18.5 mmol), and powdered molecular sieves (3 Å, 7.61 g) in CH_2Cl_2 (25 mL) was treated at 0°C with TPAP (227 mg, 0.646 mmol).[33] The resulting dark mixture was stirred at this temperature for 30 min and then at ambient temperature for 2 h. The mixture was filtered through a short silica gel column with *tert*-butyl methyl ether. The filtrates were evaporated to give crude (*R*)-*N*-(*tert*-butoxycarbonyl)-2-(2-oxoethyl)-pyrrolidine as an oil (1.91 g, 73%)[41] which was used in the next step without further purification. Characteristic data: ^{1}H NMR (400 MHz, $CDCl_3$, rotamers): δ=9.77 (t, *J*=2.0 Hz, 1H), 4.25 (m, 1H), 3.36 (m, 2H), 2.86 (m, 1H), 2.47 (ddd, *J*=16.2, 7.5, 1.7 Hz, 1H), 2.11 (m, 1H), 1.85 (m, 2H), 1.66 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=201.0, 154.4, 79.8, 52.4, 49.2, 46.4, 31.7, 28.5, 23.4; IR (film): $\tilde{\nu}$=2973, 1690, 1393, 1169 cm^{-1}; MS (EI): *m*/*z* (%): 213 (0.5) [M^+], 212 (0.5), 185 (10), 114 (34), 70 (56), 57 (100), 41 (34), 29 (10); HRMS: *m*/*z*: calcd for $C_{11}H_{19}NO_3$+Na: 236.125712; found: 236.125605.

A solution of the crude homoprolinal described above (588 mg, 2.76 mmol) and the Bestmann–Ohira reagent **24** (551 mg, 2.86 mmol)[25] in MeOH (15 mL) at 0°C was treated with K_2CO_3 (895 mg, 6.48 mmol) and the resulting mixture was allowed to slowly reach ambient temperature. After stirring for 20 h, the reaction was quenched with aq. NH_4Cl (75 mL) and water (10 mL) and extracted with *tert*-butyl methyl ether (5×15 mL). The combined extracts were washed with brine (25 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue (10% *tert*-butyl methyl ether in hexanes) gave alkyne **32** as a colorless oil which slowly solidified upon standing (317 mg, 55%). Chiral GC analysis (BGB-176SE/SE-52 column (30 m×0.25 mm, 0.25 μm stationary phase thickness), injection at 220°C, 140°C isothermal, FID detection at 320°C, 0.7 bar H_2, t_R=33.1 min (*R*), t_R=34.4 min (*S*)) showed that the product had an enantiomeric excess of > 99.5%. M.p. 52–54°C; $[\alpha]_D^{20}$=+73.5 (*c* 1.03, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, rotamers): δ=3.89 (m, 1H), 3.37 (m, 2H), 2.59 (m, 1H), 2.38 (m, 1H), 2.10–1.92 (m, 4H), 1.90–1.70 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.4, 81.7, 79.4, 69.6, 56.1, 46.9, 30.7, 29.8, 28.6, 23.2; IR (film): $\tilde{\nu}$=3243, 2969, 1678, 1396. 1171 cm^{-1}; MS (EI): *m*/*z* (%): 209 (0.4) [M^+], 170 (19), 114 (67), 70 (100), 57 (88), 41 (23), 29 (11); HRMS: *m*/*z*: calcd for $C_{12}H_{19}NO_2$+Na: 232.130794; found: 232.130771; elemental analysis calcd (%) for $C_{12}H_{19}NO_2$: C 68.87, H 9.15, N 6.69; found: C 68.81, H 9.22, N 6.58.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[3-(3′,4′,5-trimethoxybiphenyl-2-yl)-prop-2-ynyl]-pyrrolidine (33): Prepared according to the representative procedure for the 9-MeO-9-BBN mediated coupling process described above, using alkyne (*R*)-**32** (279 mg, 1.33 mmol) in THF (3 mL), *n*-BuLi (1.45 M in hexanes, 0.92 mL, 1.33 mmol), 9-MeO-9-BBN (220 mg, 1.45 mmol), iodide **20** (400 mg, 1.08 mmol), and [(dppf)$PdCl_2$] (47 mg, 0.058 mmol). Flash chromatography of the crude product (Combiflash Companion, 0→25% *tert*-butyl methyl ether in hexanes) afforded product **33** as a colorless syrup (284 mg, 0.629 mmol, 58%). Chiral HPLC analysis (Chiralcel OJ (250 mm×4.6 mm), *n*-heptane/isopropanol 9:1, 0.5 mL min^{-1}, 18.38 min (*R* isomer), 48.27 min (*S* isomer)) showed that the product had an enantiomeric excess of > 98%. $[\alpha]_D^{20}$+45.6 (*c* 1.19, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, rotamers): δ=7.42 (d, *J*=8.5 Hz, 1H), 7.14 (m, 1H), 7.11 (dd, *J*=8.2, 1.7 Hz, 1H), 6.92 (d, *J*=8.2 Hz, 1H), 6.88 (d, *J*=2.6 Hz, 1H), 6.70 (dd, *J*=8.5, 2.5 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.82 (s, 3H), 3.78 (m, 1H), 3.4–3.3 (m, 2H), 2.8–2.6 (m, 1H), 2.44 (m, 1H), 1.9–1.6 (m, 4H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, rotamers): δ=158.8, 154.0, 148.1, 147.9, 144.6, 134.2, 133.2, 121.1, 114.5, 114.2, 113.9, 112.4, 112.1, 110.4, 88.3, 87.9, 81.1, 80.8, 79.0, 78.7, 55.9, 55.6, 55.0, 46.6, 46.3, 30.2, 29.4, 28.2, 24.7, 24.0, 23.2, 22.4; IR (film): $\tilde{\nu}$=2969, 1690, 1603, 1393, 1365, 1254, 1167, 1029 cm^{-1}; MS (EI): *m*/*z* (%): 451 (23) [M^+], 378 (8), 282 (16), 281 (12), 170 (30), 114 (100), 70 (74), 57 (35), 41 (5); HRMS: *m*/*z*: calcd for $C_{27}H_{33}NO_5$+Na: 474.225096; found: 474.225134; elemental analysis calcd (%) for $C_{27}H_{33}NO_5$: C 71.82, H 7.37, N 3.10; found: C 71.88, H 7.43, N 2.96.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[(2,3,6-trimethoxyphenanthren-10-yl)-methyl]-pyrrolidine (34): Prepared according to the representative procedure for the cycloisomerization described above, upon treatment of a solution of substrate **33** (194 mg, 0.430 mmol) with $PtCl_2$ (30 mg, 0.11 mmol) in toluene (43 mL) at 60°C for 1 h and then at 80°C for 3 h. Flash chromatography (Combiflash Companion, 0→30% *tert*-butyl methyl ether in hexanes) of the crude product gave phenanthrene **34** as an oil which slowly solidified upon standing (141 mg, 72%). Chiral HPLC analysis (Chiralcel OD-H (250 mm×4.6 mm), *n*-heptane/isopropanol 98:2, 0.5 mL min^{-1}, 28.07 min (*R* isomer), 33.85 min (*S* isomer)) showed that the product had an enantiomeric excess of > 98%. M.p. 99–101°C; $[\alpha]_D^{20}$=−72.1 (*c* 1.07, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, rotamers): δ=8.32 (brs, 1H), 7.91 (s, 1H), 7.84 (d, *J*=2.3 Hz, 1H), 7.72 (d, *J*=8.7 Hz, 1H), 7.38 (s, 1H), 7.16 (dd, *J*=8.7, 2.3 Hz, 1H), 4.26 (m, 1H), 4.20 (brs, 3H), 4.11 (s, 3H), 4.01 (s, 3H), 3.90 (m, 1H), 3.48 (m, 1H), 3.35 (m, 1H), 2.62 (m, 1H), 2.00 (m, 1H), 1.82 (m, 2H), 1.66 (m, 1H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=157.8, 154.7, 149.8, 148.8, 131.0, 130.6, 129.6, 127.3, 126.0, 125.8, 124.6, 115.3, 106.8, 103.9, 103.5, 79.0, 57.3, 56.7, 56.0, 55.6, 46.8, 38.5, 29.1, 28.6, 23.4; IR (film): $\tilde{\nu}$=2927, 1684, 1609, 1394, 1260, 1160, 1029, 799 cm^{-1}; MS (EI): *m*/*z* (%): 451 (37) [M^+], 378 (7), 282 (33), 281 (77), 170 (18), 114 (100), 70 (72), 57 (52), 41(14); HRMS: *m*/*z*: calcd for $C_{27}H_{33}NO_5$+Na: 474.225093; found: 474.224895; elemental analysis calcd (%) for $C_{27}H_{33}NO_5$: C 71.82, H 7.37, N 3.10; found: C 71.68, H 7.32, N 3.15.

(−)-Antofine (2): A solution of phenanthrene **34** (122 mg, 0.271 mmol) in EtOH (12 mL) was treated with aqueous HCHO (37% *w*/*w*, 2.2 mL, 27 mmol) and HCl (12 M, 0.4 mL, 5 mmol) and the resulting mixture was stirred at 80°C in the dark for 43 h. The solvents were evaporated and the residue was taken up in NaOH (6 M, 5 mL) and extracted with CH_2Cl_2 (4×5 mL). The combined extracts were washed with water (4×5 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated to give the title compound as a powder (90 mg, 0.25 mmol, 91%). Chiral HPLC analysis (Chiralpak AD-H (250 mm×4.6 mm), *n*-heptane/isopropanol 4:1, 0.5 mL min^{-1}, 33.39 min (*S* isomer), 49.72 min (*R* isomer)) showed that the product had an enantiomeric excess of > 98%. $[\alpha]_D^{20}$=−113.4 (*c* 1.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.93 (s, 1H), 7.92 (d, *J*=2.6 Hz, 1H), 7.83 (d, *J*=9.0 Hz, 1H), 7.32 (s, 1H), 7.22 (dd, *J*=9.0, 2.6 Hz, 1H), 4.71 (d, *J*=14.8 Hz, 1H), 4.12 (s, 3H), 4.08 (s, 3H), 4.03 (s, 3H), 3.72 (d, *J*=15.0 Hz, 1H), 3.47 (m, 1H), 3.37 (dd, *J*=15.8, 2.4 Hz, 1H), 2.92 (m, 1H), 2.47 (m, 2H), 2.26 (m, 1H), 2.05 (m, 1H), 1.92 (m, 1H), 1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=157.6, 149.5, 148.5, 130.3, 127.0, 126.3, 125.5, 124.3, 124.1, 123.6, 115.0, 104.7, 104.0, 103.9, 60.3, 56.1, 55.9, 55.6, 55.1, 53.7, 33.5, 31.3, 21.6; IR (film): $\tilde{\nu}$=2913, 1614, 1510, 1205, 1032, 840, 830, 808, 780 cm^{-1}; MS (EI): *m*/*z* (%): 363 (28) [M^+], 294 (100), 279 (7), 251 (5); HRMS: *m*/*z*: calcd for $C_{23}H_{26}NO_3$: 364.190721; found: 364.190408.

Tylophorine series

1,2-Dimethoxy-4-iodobenzene (36):[36] A purple solution of veratrole **35** (2.10 g, 15.23 mmol) and iodine (4.23 g, 16.7 mmol) in CH_2Cl_2 (60 mL) was treated with red HgO (3.58 g, 16.5 mmol). After stirring for 5 h, the mixture was filtered through Celite and the filtrate was washed with aq. $Na_2S_2O_3$ (5% *w*/*w*, 4×15 mL) and brine (50 mL) before being dried (Na_2SO_4) and concentrated to a reddish oil which could be used without further purification (3.90 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.22 (dd, *J*=8.5, 2.1 Hz, 1H), 7.12 (d, *J*=2.1 Hz, 1H), 6.62 (d, *J*=8.4 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.8, 149.2, 129.8, 120.4, 113.2, 82.3, 56.1, 55.9; IR (film): $\tilde{\nu}$=3076, 2999, 1583, 1501, 1250, 839, 798, 762 cm^{-1}; MS (EI): *m*/*z* (%): 264 (100) [M^+], 249 (28), 221 (8), 94 (26); HRMS (EI): *m*/*z*: calcd for $C_8H_9IO_2$: 263.964730; found: 263.964440.

2-Bromo-3′,4,4′,5-tetramethoxybiphenyl (39): A solution of iodoveratrole **36** (3.90 g, 14.8 mmol) in HOAc (4 mL) was treated dropwise with a solution of bromine (1.0 mL, 19 mmol) in HOAc (5 mL). After stirring for 3 h, the dark mixture was diluted with water (50 mL) and extracted with *tert*-butyl methyl ether (4×15 mL). The combined organic layers were washed with aq. sat. $NaHCO_3$ (25 mL), aq. $Na_2S_2O_3$ (10%, 6×10 mL) and brine (25 mL), before being dried (Na_2SO_4) and evaporated. Recrystallization of the crude product from ethanol afforded reddish-white crystals of 1-iodo-2-bromo-4,5-dimethoxybenzene (**37**) (3.37 g, 67%) which were contaminated with ~15% of a dibromide. This product was used in the next step without further purification. Characteristic data: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.22 (s, 1H), 7.07 (s, 1H), 3.85 (s, 3H), 3.84 (s, 3H).

A mixture of crude iodide **37** (689 g, 2.01 mmol), boronic acid **38** (396 mg, 2.18 mmol), LiCl (256 mg, 6.04 mmol), degassed aq. Na_2CO_3 (2 M, 5.0 mL, 10 mmol), and [(dppf)$PdCl_2$] (89 mg, 0.11 mmol) in DME (15 mL) was stirred at 80 °C for 16 h. The mixture was cooled to ambient temperature, diluted with aq. NH_4Cl (50 mL) and extracted with *tert*-butyl methyl ether (4×25 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. Evaporation of the solvents afforded the crude product as a dark oil which was purified by flash chromatography (Combiflash Companion, 0→25% *tert*-butyl methyl ether in hexanes) to give biaryl **39** as a colorless oil which slowly solidified upon standing (423 mg, 59%). The analytical data for this compound matched the published data.[42] M.p. 84–85 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.12 (s, 1H), 6.95–6.93 (m, 3H), 6.84 (s, 1H), 3.93 (s, 3H), 3.91 (m, 6H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=148.6, 148.4, 148.2, 134.6, 133.8, 121.8, 115.8, 114.0, 113.1, 112.7, 110.7, 56.2, 56.1, 56.0, 55.9; IR (KBr): 3057, 2936, 1600, 1499, 1248, 1027 cm^{-1}; MS (EI): *m*/*z* (%): 354 (99) [*M*(^{81}Br)$^+$], 352 (100) [*M*(^{79}Br)$^+$], 339 (11), 337 (11), 311 (7), 309 (8), 230 (16); HRMS: *m*/*z*: calcd for $C_{16}H_{17}{}^{79}BrO_4$+Na 375.020257; found: 375.020196.

2-Iodo-3′,4,4′,5-tetramethoxybiphenyl (40): A solution of bromide **39** (199 mg, 0.564 mmol) in THF (5 mL) at −78 °C was treated with *n*-BuLi (1.6 M in hexanes, 0.45 mL, 0.72 mmol) and stirred for 45 min. The resulting dark yellow solution was treated with a solution of I_2 (212 mg, 0.835 mmol) in THF (2.5 mL), stirred at −78 °C for a further 5 min, and then stirred at ambient temperature for 45 min. The resulting dark solution was quenched with aq. sat. NH_4Cl (5 mL) and extracted with *tert*-butyl methyl ether (4×5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated to a yellow oil (192 mg) which was purified by flash chromatography (Combiflash Companion, 0→30% *tert*-butyl methyl ether/hexane) to give product **40** as an oil which solidified over time (123 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.33 (s, 1H), 6.93–6.86 (m, 3H), 6.84 (s, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 149.1, 148.6, 148.4, 148.2, 139.1, 137.0, 121.7, 121.6, 113.1, 113.0, 110.6, 86.8, 56.3, 56.00, 55.99, 55.9; IR (film): $\tilde{\nu}$=2933, 1593, 1495, 1244, 1025 cm^{-1}; MS (EI): *m*/*z* (%): 400 (100) [*M*$^+$], 385 (9), 357 (5), 273 (1), 215 (8); HRMS: *m*/*z*: calcd for $C_{16}H_{17}IO_4$+Na: 423.006375; found: 423.006276.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[3-(3′,4,4′,5-tetramethoxy-biphenyl-2-yl)-prop-2-ynyl]-pyrrolidine (41): Prepared according to the representative procedure for the 9-MeO-9-BBN mediated coupling outlined above, using alkyne (*R*)-**32** (93 mg, 0.45 mmol) in THF (1 mL), *n*-BuLi (1.6 M in hexanes, 0.26 mL, 0.42 mmol), 9-MeO-9-BBN (82 mg, 0.54 mmol), iodide **40** (123 mg, 0.307 mmol, added as a solution in 2 mL THF), and [(dppf)$PdCl_2$] (14 mg, 0.018 mmol). Work up after 20 h gave the crude product as a dark oil which was purified by flash chromatography (Combiflash Companion, 0→50% *tert*-butyl methyl ether in hexane) to give product **41** as a syrup (35 mg, 64% based on recovered iodide **40** (51 mg, 42%)). $[\alpha]_D^{20}$=+47.5 (*c* 1.32, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.13 (m, 1H), 7.07 (dd, *J*=8.2, 2.1 Hz, 1H), 6.98 (s, 1H), 6.91 (d, *J*= 7.8 Hz, 1H), 6.82 (s, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.80 (m, 1H), 3.40–3.22 (m, 2H), 2.91–2.62 (m, 1H), 2.44 (m, 1H), 1.90–1.60 (m, 4H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.5, 149.0, 148.3, 147.7, 137.2, 137.0, 133.7, 129.1, 121.5, 115.4, 113.8, 112.9, 112.4, 110.8, 88.7, 88.2, 81.7, 81.2, 79.5, 79.1, 56.3, 56.1, 56.0, 47.0, 46.7, 30.6, 29.7, 28.6, 25.0, 24.3, 23.5, 22.9; IR (film): $\tilde{\nu}$=2931, 1687, 1602, 1503, 1391, 1364, 1250, 1027, 858 cm^{-1}; MS (EI): *m*/*z* (%): 481 (24) [*M*$^+$], 408 (5), 312 (12), 311 (6), 280 (15), 170 (16), 114 (100), 70 (92), 57 (48), 41 (7); HRMS: *m*/*z*: calcd for $C_{28}H_{35}NO_6$+Na 504.235655; found: 504.235686.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[(2,3,6,7-tetramethoxy-phenanthren-10-yl)methyl]-pyrrolidine (42): A solution of alkyne **41** (35 mg, 0.073 mmol) in toluene (1.5 mL) was treated with $PtCl_2$ (4 mg, 0.02 mmol) and the resulting mixture was stirred at 60 °C for 2 h and then at 80 °C for 1 h. The mixture was then absorbed onto silica gel and eluted through a pad of silica gel (10% EtOAc in toluene) to give phenanthrene **42** as an oil (20 mg, 56%). $[\alpha]_D^{20}$=−11.3 (*c* 0.99, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, rotamers): δ=8.31 (brs, 1H), 7.82 (brs, 1H), 7.78 (s, 1H), 7.37 (s, 1H), 7.17 (s, 1H), 4.21–3.90 (m, 2H), 4.21 (brs, 3H), 4.13 (s, 3H), 4.11 (s, 3H), 4.03 (s, 3H), 3.49 (m, 1H), 3.33 + 2.99 (m, 1H), 2.60 (m, 1H), 2.02 (m, 1H), 1.84 (m, 2H), 1.62 (m, 1H), 1.52 (brs, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.7, 149.1, 149.0, 148.9, 148.7, 131.8, 126.24, 126.16, 125.3, 124.7, 123.9, 107.9, 106.8, 102.9, 79.0, 57.4, 56.7, 56.2, 56.0, 55.9, 46.9, 38.6, 29.1, 28.6, 23.5; IR (film): $\tilde{\nu}$=2932, 1685, 1619, 1396, 1253, 1150 cm^{-1}; MS (EI): *m*/*z* (%): 481 (40) [*M*$^+$], 408 (6), 312 (32), 311 (72), 170 (16), 114 (100), 70 (71), 57 (40), 41 (6); HRMS: *m*/*z*: calcd for $C_{28}H_{35}NO_6$+Na: 504.235659; found: 504.235438.

(−)-Tylophorine (3): Prepared according to the representative procedure for the deprotection/Pictet–Spengler tandem, using phenanthrene **42** (17 mg, 0.035 mmol), aq. HCHO (37% *w*/*w*, 0.30 mL, 3.7 mmol) and HCl (12 M, 50 μL, 0.60 mmol) in EtOH (1.5 mL). Reaction time: 23 h; the crude product was purified by flash chromatography (10% EtOH in CH_2Cl_2) to give tylophorine as a pale brown powder (6.5 mg, 48%). $[\alpha]_D^{20}$=−77.6 (*c* 0.65, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.84 (s, 1H), 7.83 (s, 1H), 7.32 (s, 1H), 7.17 (s, 1H), 4.64 (d, *J*=14.7 Hz, 1H), 4.11 (m, 6H), 4.06 (s, 3H), 4.05 (s, 3H), 3.68 (d, *J*=15.9 Hz, 1H), 3.48 (m, 1H), 3.38 (dd, *J*=16.6, 2.9 Hz, 1H), 2.92 (m, 1H), 2.50 (m, 2H), 2.24 (m, 1H), 1.99 (m, 2H), 1.77 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 148.8, 148.6, 148.5, 126.4, 126.1, 125.9, 124.4, 123.7, 123.5, 104.1, 103.6, 103.5, 103.3, 60.3, 56.1, 56.0, 55.9, 55.2, 54.1, 33.8, 31.3, 21.7; IR (film): $\tilde{\nu}$=2830, 1618, 1512, 1244, 1207, 1148, 1017, 841 cm^{-1}; MS (EI): *m*/*z* (%): 393 (27) [*M*$^+$], 324 (100), 309 (7), 162 (8); HRMS (ES, *m*/*z*) calcd for $C_{24}H_{28}NO_4$: 394.201282; found: 394.201207.

Ficuseptine C series

2-Bromo-3′,4′-methylenedioxy-5-methoxybiphenyl (44): A mixture of iodide **17** (630 mg, 2.01 mmol), boronic acid **43** (352 mg, 2.12 mmol), LiCl (322 mg, 7.60 mmol), degassed aq. Na_2CO_3 (2 M, 4 mL, 8 mmol), and [(dppf)$PdCl_2$] (84 mg, 0.103 mmol) in DME (15 mL) was stirred at 80 °C for 20 h. The mixture was cooled to ambient temperature, diluted with aq. NH_4Cl (50 mL) and extracted with *tert*-butyl methyl ether (4× 25 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. Evaporation of the solvents afforded the crude product as a dark oil which was purified by flash chromatography (Combiflash Companion, 0→5% *tert*-butyl methyl ether in hexanes) to give biaryl **44** as a light yellow oil (278 mg, 45%) which was further purified by Kugelrohr distillation (250 °C, 0.1 Torr) to give the product as a colorless oil (251 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.48 (d, *J*= 8.8 Hz, 1H), 6.89 (m, 1H), 6.83 (m, 3H), 6.72 (dd, *J*=8.8, 3.1 Hz, 1H), 5.97 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=158.7, 147.13, 147.11, 142.9, 134.9, 133.6, 122.8, 116.8, 114.5, 113.2, 110.0, 107.9, 101.2, 55.4; IR (film): $\tilde{\nu}$=3002, 2892, 1590, 1566, 1463, 1226, 1026, 804 cm^{-1}; MS (EI): *m*/*z* (%): 308 (99) [*M*(^{81}Br)$^+$], 306 (100) [*M*(^{79}Br)$^+$], 265 (7), 263 (7), 126 (25); HRMS (EI): *m*/*z*: calcd for $C_{14}H_{11}{}^{79}BrO_3$: 305.989169; found: 305.989001; elemental analysis calcd (%) for $C_{14}H_{11}{}^{79}BrO_3$: C 54.75, H 3.61; found: C 54.76, H 3.57.

2-Iodo-3′,4′-methylenedioxy-5-methoxybiphenyl (45): A solution of bromide **44** (251 mg, 0.743 mmol) in THF (8 mL) at −78 °C was treated with *n*-BuLi (1.6 M in hexanes, 0.56 mL, 0.90 mmol) and stirred for 15 min. Solid I_2 (270 mg, 1.06 mmol) was added to the bright yellow solution, and the resulting dark mixture was stirred at −78 °C for 15 min and then at ambient temperature for 1 h. The reaction was quenched with aq. $Na_2S_2O_3$ (1 M, 5 mL) and extracted with *tert*-butyl methyl ether (4× 5 mL). The combined organic phases were washed with water (5 mL) and

brine (5 mL) before they were dried (Na_2SO_4) and evaporated. Flash chromatography (toluene/hexane 1:1) gave product **45** as a colorless oil (220 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, J = 8.7 Hz, 1H), 6.87–6.85 (m, 2H), 6.82 (d, J = 1.6 Hz, 1H), 6.78 (dd, J = 7.9 Hz, 1.7 Hz, 1H), 6.63 (dd, J = 8.7 Hz, 3.0 Hz, 1H), 6.02 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 147.1, 147.07, 147.0, 139.9, 138.0, 122.8, 116.0, 115.1, 109.9, 107.9, 101.2, 87.5, 55.4; IR (film): $\tilde{\nu}$ = 3002, 2889, 1584, 1225, 1036, 805 cm^{-1}; MS (EI): m/z (%): 354 (100) [M^+], 212 (6), 197 (10), 169 (12), 139 (11), 126 (16); elemental analysis calcd (%) for $C_{14}H_{11}IO_3$: C 47.48, H 3.13; found: C 47.43, H 3.08.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[3-(3′,4′-methylenedioxy-5-methoxybiphenyl-2-yl)-prop-2-ynyl]-pyrrolidine (46): Prepared according to the representative procedure for the 9-MeO-9-BBN mediated cross-coupling, using alkyne (*R*)-**32** (156 mg, 0.745 mmol) and *n*-BuLi (1.6 M in hexanes, 0.46 mL, 0.74 mmol) in THF (1.5 mL), 9-MeO-9-BBN (137 mg, 0.90 mmol), [(dppf)$PdCl_2$] (24 mg, 0.030 mmol), and iodide **45** (204 mg, 0.575 mmol, added as a solution in 4 mL THF). Work-up after 20 h as described afforded a yellow oil which was purified by flash chromatography (Combiflash Companion, 0→25% *tert*-butyl methyl ether in hexanes) to give product **46** as a syrup (148 mg, 59%). $[\alpha]_D^{20}$ = +39.6 (*c* 1.15, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, rotamers): δ = 7.41 (d, J = 8.5 Hz, 1H), 7.08 (m, 1H), 7.02 (m, 1H), 6.85 (d, J = 7.8 Hz, 1H), 6.83 (d, J = 2.5 Hz, 1H), 6.79 (dd, J = 8.4, 2.5 Hz, 1H), 6.00 (s, 2H), 3.90–3.81 (m, 1H), 3.83 (s, 3H), 3.4–3.2 (m, 2H), 2.9–2.6 (m, 1H), 2.46 (m, 1H), 1.84 (m, 3H), 1.67 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers): δ = 159.1, 154.4, 147.2, 147.0, 144.8, 134.8, 134.5, 122.7, 114.8, 114.4, 112.7, 109.9, 107.9, 101.0, 88.8, 88.5, 81.2, 81.0, 79.4, 79.2, 70.9, 56.3, 55.4, 47.0, 46.7, 32.1, 30.6, 29.8, 28.6, 26.3, 25.1, 24.4, 23.6, 22.9, 22.1; IR (film): $\tilde{\nu}$ = 2926, 1688, 1600, 1391, 1364, 1237, 1038, 809 cm^{-1}; MS (EI): m/z (%): 435 (9) [M^+], 266 (11), 170 (27), 114 (100), 70 (77), 57 (51), 41 (8); HRMS: m/z: calcd for $C_{26}H_{29}NO_5$ + Na: 458.193790; found: 458.193851.

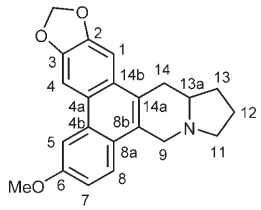
(*R*)-*N*-(*tert*-Butoxycarbonyl)-2-[(2,3-methylenedioxy-6-methoxy-phenanthren-10-yl)methyl]-pyrrolidine (47): A solution of compound **46** (148 mg, 0.340 mmol) in toluene (7 mL) was treated with $PtCl_2$ (19 mg, 0.71 mmol) and the resulting mixture was stirred at 60 °C for 2 h and then at 80 °C for additional 20 h. The mixture was then passed through a plug of silica (EtOAc), the filtrate was evaporated and the residue was purified by flash chromatography (5→10% EtOAc in toluene) to give phenanthrene **47** as a pale yellow powder (83 mg, 56%). M.p. 78–80 °C; $[\alpha]_D^{20}$ = −28.0 (*c* 1.06, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, rotamers): δ = 8.08 and 7.74 (br s, 1H), 7.97 (s, 1H), 7.78 (d, J = 2.2 Hz, 1H), 7.71 (d, J = 8.9 Hz, 1H), 7.39 (s, 1H), 7.17 (dd, J = 8.6, 2.2 Hz, 1H), 6.11 (s, 2H), 4.25 (m, 1H), 4.00 (s, 3H), 3.92–3.62 (m, 1H), 3.60–3.20 (m, 2H), 2.69 (dd, J = 13.5, 10.6 Hz, 1H), 2.11–1.91 (m, 1H), 1.90–1.70 (m, 2H), 1.70–1.40 (m, 1H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.0, 154.7, 148.0, 147.4, 131.2, 130.7, 130.6, 129.5, 128.2, 126.6, 126.2, 126.1, 126.0, 116.4, 103.6, 103.2, 102.8, 101.4, 101.2, 100.9, 80.1, 79.0, 57.2, 56.5, 55.4, 46.9, 46.6, 38.8, 38.0, 29.6, 28.8, 28.7, 23.5, 22.5; IR (CH_2Cl_2): $\tilde{\nu}$ = 2971, 1682, 1614, 1473, 1392, 1231, 1038, 834 cm^{-1}; MS (EI): m/z (%): 435 (28) [M^+], 362 (7), 266 (28), 265 (72), 170 (21), 114 (100), 70 (78), 57 (49), 41 (8); HRMS: m/z: calcd for $C_{26}H_{29}NO_5$ + Na 458.193794; found: 458.193680; elemental analysis calcd (%) for $C_{26}H_{29}NO_5$: C 71.70, H 6.71, N 3.22; found: C 71.63, H 6.66, N 3.24.

(−)-Ficuseptine C (4): Prepared according to the general procedure for the deprotection/Pictet-Spengler tandem described above, using phenanthrene **47** (79 mg, 0.181 mmol), aq. HCHO (37% *w*/*w*, 1.5 mL, 18 mmol) and HCl (12 M, 0.25 mL, 3.0 mmol) in EtOH (8.5 mL). Workup after 3 d afforded the crude product as a brown powder which was purified by flash chromatography (5% EtOH in CH_2Cl_2) to give ficuseptine C as a beige powder (39 mg, 62%). M.p. 193–195 °C (decomp); $[\alpha]_D^{25}$ = −26 (*c* 0.06, MeOH), −129.7 (*c* 1.05, $CHCl_3$). For a compilation of the spectroscopic data, see Table 1.

X-ray crystal structure analysis of phenanthrene 28: $C_{28}H_{35}NO_5$, M_r = 465.57, colorless plate, crystal size 0.08 × 0.02 × 0.02 mm, monoclinic, space group $P2_1/c$, a = 18.5321(10), b = 6.2770(3), c = 21.1387(13) Å, β = 94.466(3)°, V = 2451.5(2) Å^3, T = 100 K, Z = 4, ρ_{calcd} = 1.261 g cm^{-3}, λ = 0.71073 Å, $\mu(Mo_{K\alpha})$ = 0.086 mm^{-1}, Nonius KappaCCD diffractometer, 4.08 < θ < 24.03, 19361 measured reflections, 3835 independent reflections, 2117 reflections with $I > 2\sigma(I)$, structure solved by direct methods and refined by full-matrix least-squares against F^2 to R_1 = 0.062 [$I > 2\sigma(I)$], wR_2 = 0.176, 313 parameters, H atoms riding, S = 0.908, residual electron density +0.2/−0.3 e Å^{-3}.

CCDC-603030 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 1. Tabular survey of the NMR spectroscopic data of ficuseptine C (**4**). Unless stated otherwise, all assignments are unambiguous (cf. general methods); numbering scheme as shown in the insert; the reported coupling constants are not averaged.



(-)-ficuseptine C (**4**)

Position	^{13}C NMR (100 MHz): δ		^{1}H NMR (400 MHz, $CDCl_3$): δ (J in Hz)
	[D_6]acetone	$CDCl_3$	
1	102.0	101.5	7.34 (s)
2	149.0	147.8[a]	
3	148.1	147.0[a]	
4	102.1	101.1	7.92 (s)
4a	126.0	125.0	
4b	131.5	130.4	
5	104.8	104.0	7.80 (d, J = 2.4 Hz)
6	158.8	157.5	
7	117.1	115.8	7.16 (dd, J = 2.4, 9.0 Hz)
8	125.0	124.2	7.76 (d, J = 9.0 Hz)
8a	124.8	124.1	
8b	128.0	126.7	
9	54.5	53.8	4.64 (dd, J = < 1, 15.0 Hz) 3.64 (ddd, J = 1.8, 2.4, 15.0 Hz)
11	55.6	55.1	3.43 (dt, J = 2.0, 8.7 Hz) 2.41 (q, J = 9.0 Hz)
12	22.2	21.6	2.00 (tdt, J = 4.2, 8.7, 12.0 Hz) 1.88 (ddddd, J = 2.3, 6.5, 9.0, 10.0, 12.0 Hz)
13	32.0	31.3	2.20 (dddd, J = 4.2, 6.8, 10.0, 12.2 Hz) 1.72 (ddt, J = 6.4, 9.6, 11.7 Hz)
13a	61.1	60.2	2.43 (dddd, J = 4.0, 7.0, 9.6, 10.4 Hz)
14	34.7	34.0	3.25 (ddd, J = 1.6, 3.9, 16.0 Hz) 2.84 (dddd, J = 1.6, 2.2, 10.4, 16.0 Hz)
14a	126.9	125.9	
14b	129.3	128.5	
-OCH_2O-	102.0	101.3	6.07 (s, 2H)
MeO-	55.8	55.4	3.97 (s, 3H)

[a] These assignments can be interchangeable.

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experiments and technical assistance, Mrs. A. Dreier and Dr. C. W. Lehmann for the crystal structure analysis of **28**, and Umicore AG & CoKG, Hanau, for a generous donation of noble metal salts.

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