ChemPubSoc Europe

DOI: 10.1002/chem.201705575

CHEMISTRY A European Journal Communication

Bioactive Compounds

Total Synthesis of Sarpagine-Related Bioactive Indole Alkaloids

M. Toufiqur Rahman,[a] Jeffrey R. Deschamps,[b] Gregory H. Imler,[b] and James M. Cook*[a]

Abstract: Extension of the asymmetric Pictet–Spengler reaction to bulkier N_b-alkylated tryptophan derivatives resulted in an improved stereospecific access to the key bicyclo[3.3.1]nonane core of bioactive C-19 methyl substituted sarpagine/macroline/ajmaline indole alkaloids with excellent diastereoselectivity by internal asymmetric induction. Complete stereocontrol of the C-19 methyl function in either the α- or β-configuration was achieved, which enables the total synthesis of any member from this group of thirty alkaloids. We report herein, the total synthesis of macrocarpines (A-C) **1**–**3**, talcarpine **4**, *N*(4)-methyl-*N*(4),21-*seco*talpinine **5**, dihydroperaksine **8** and deoxyperaksine **9**.

The C-19 methyl substituted macroline/sarpagine and ajmaline alkaloids are an emerging group of biosynthetically related indole alkaloids, some of which have historical significance,[1] and have been primarily isolated from various medicinal plants of the *Apocynaceae* family. Currently, about thirty alkaloids belong to this group. Some of them are depicted in Figure 1. Most of these alkaloids have not been tested for their biological activity, presumably due to the paucity of isolated material. Yet, some of these alkaloids have been shown to possess important biological activity ranging from anti-hypertensive to anticancer properties. Macrocarpines A-C (**1**–**3**) have been isolated from the stem bark of *Alstonia macrophylla* by Kam.[2] Talcarpine (**4**), which was isolated from *Alstonia* macrophylla and *Pleiocarpa talbotii*, exhibited antimalarial activity.[3] *N*(4)-Methyl-*N*(4),21-*seco*talpinine **5**, isolated from *Pleiocarpa talbotii,* and *Alstonia angustifolia*, demonstrated promising *anti*-leishmanial activity.[2,3b,4] Talpinine **6**, another related alkaloid, showed moderate activity in reversing multidrug-resistance in a vincristine-resistant KB/VJ300 cell line in the presence of 0.12 μM vincristine.[3b,5] *N*(4)-Methyltalpinine **7**, which contains a quaternary N_b-nitrogen atom, is the N_b-methylated version of talpinine **6**, and has shown potent and important NF*k*B inhibition.[4] Although the majority of these alkaloids have the β-methyl configuration at C-19, a few contain the α C-19 methyl function (e.g., dihydroperaksine **8**, also known as dihydrovomifoline and deoxyperaksine **9**).[6] All of these alkaloids bear either an N_a-methyl or N_a-hydrogen-substituted indole nitrogen atom. Similarly, the N_b-nitrogen atom also varies in the pattern of substitution. In addition, all of these alkaloids contain 6 or 7 quaternary centers with various substitution patterns and configurations, which renders the synthesis of these alkaloids of interest. The challenge to access the complex architecture of these alkaloids and their promising biological activity stimulated our interest in the total synthesis of these natural products by a general strategy. To illustrate the feasibility of this strategy to access either the α or β C-19 methyl-substituted alkaloids stereospecifically, we report the total synthesis of (−)-macrocarpines A-C (**1**–**3**), (−)-talcarpine (**4**), (+)-*N*(4)-methyl-*N*(4),21-*seco*talpinine (**5**), (+)-dihydroperaksine (**8**) and (−)-deoxyperaksine (**9**) with complete stereocontrol of the methyl function at C-19.

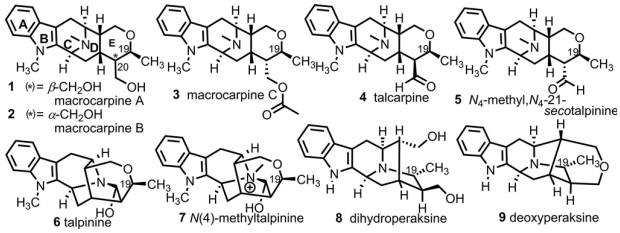


Figure 1. Representative examples of chiral C-19 methyl substituted macroline/sarpagine alkaloids.

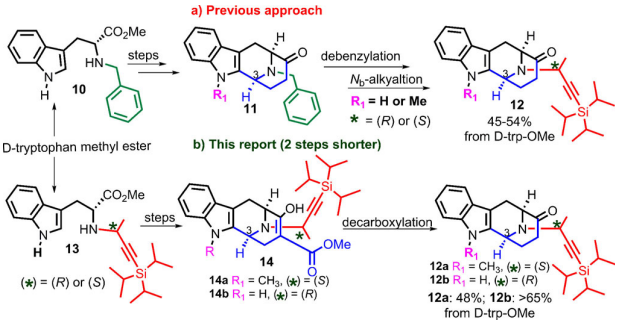
The Pictet–Spengler reaction is among the most useful reactions in organic chemistry and probably the best one to access the tetrahydro-β-carboline and tetrahydroisoquinoline systems.[7] The asymmetric version of this reaction has been used in numerous instances for stereospecific access to this system and has been key to the total synthesis of numerous indole, bisindole, and oxindole alkaloids.[8] In this vein, the synthesis of numerous alkaloids of the sarpagine, macroline, ajmaline group, have been accessed by the *trans*-diester/Dieckmann protocol, in excellent yield and with 100% diastereoslectivity.[7b,9] This diastereospecific cyclization reaction sets the required stereochemistry at the C-3 position for the target natural products, beginning with commercially available D-(+)-tryptophan.[7b,9a]

In the present report, extension of the asymmetric Pictet–Spengler reaction to other N_b-alkyl systems was explored. The N_b-alkylated compounds (see **12**, Scheme 1) are key intermedi-

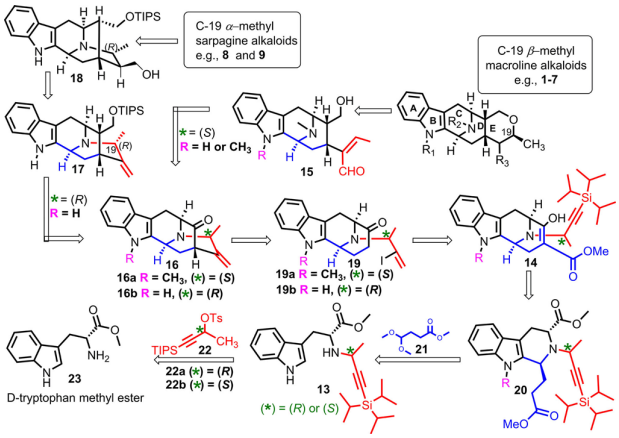
[a] *M. T. Rahman, Prof. Dr. J. M. Cook*
Department of Chemistry and Biochemistry
University of Wisconsin-Milwaukee
3210 N Cramer Street, Milwaukee, WI 53201 (USA)
E-mail: capncook@uwm.edu

[b] *Dr. J. R. Deschamps, Dr. G. H. Imler*
Center for Biomolecular Science and Engineering
Naval Research Laboratory, Code 6930
Washington, DC 20375 (USA)

Supporting Information and the ORCID number(s) for the author(s) of this article can be found under https://doi.org/10.1002/chem.201705575.



Scheme 1. Stereospecific access to the bicyclo[3.3.1]nonane system **12**.



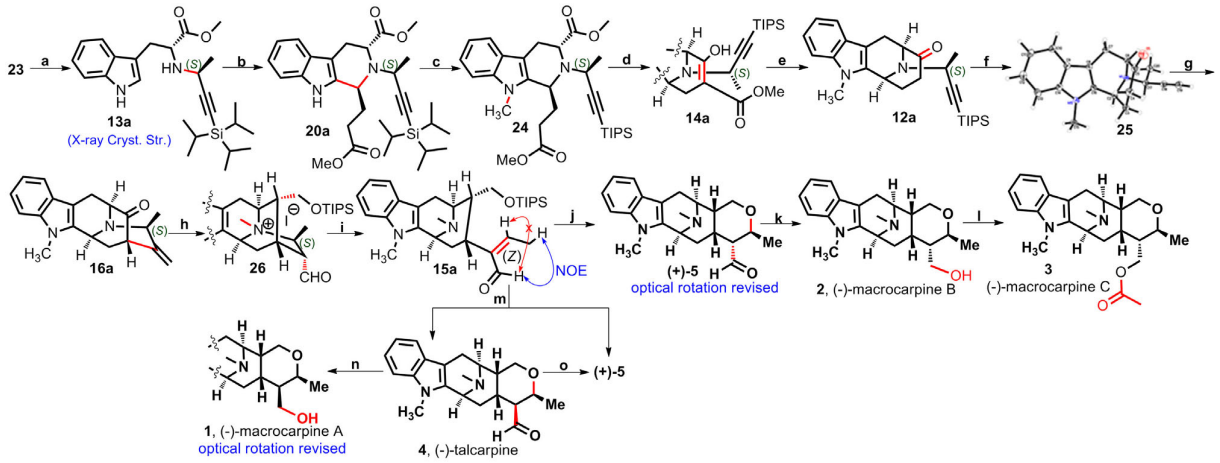
Scheme 2. Retrosynthetic analysis for the total synthesis of the C-19 methyl substituted macroline/sarpagine-related alkaloids via the asymmetric Pictet-Spengler reaction.

ates that have been used in the total synthesis of several sarpagine and macroline related indole alkaloids, which contain a stereogenic methyl function at the C-19 position of the core structure.[10] In the strategy developed by Edwankar et al.,[10] the N_b-alkyl tethered functionality was introduced after accessing the bicyclo[3.3.1]nonane system in **11**. Despite the robustness of this strategy (Scheme 1 a), it was deemed useful to reduce the number of steps by avoiding some earlier transformations while retaining compatibility with various conditions necessary for accessing the desired system in high enantiomeric (*ee*) and diastereomeric excess (*de*). In this respect, the strategy was to avoid the initial benzylation and later debenzylation by simply alkylating the N_b-nitrogen atom at the beginning of the synthesis (Scheme 1 b). It would be advantageous if this could be done in stereospecific fashion. This would shorten the synthesis by 2 steps but still retain the robust nature of the route. In addition, as mentioned, this would expand the use of the asymmetric Pictet–Spengler reaction and the Dieckmann cyclization with the bulky TIPS-protected ethinyl N_b-alkyl system. The target system **12** would be accessible simply by decarboxylation of the products (see **14**) from the Dieckmann cyclization.

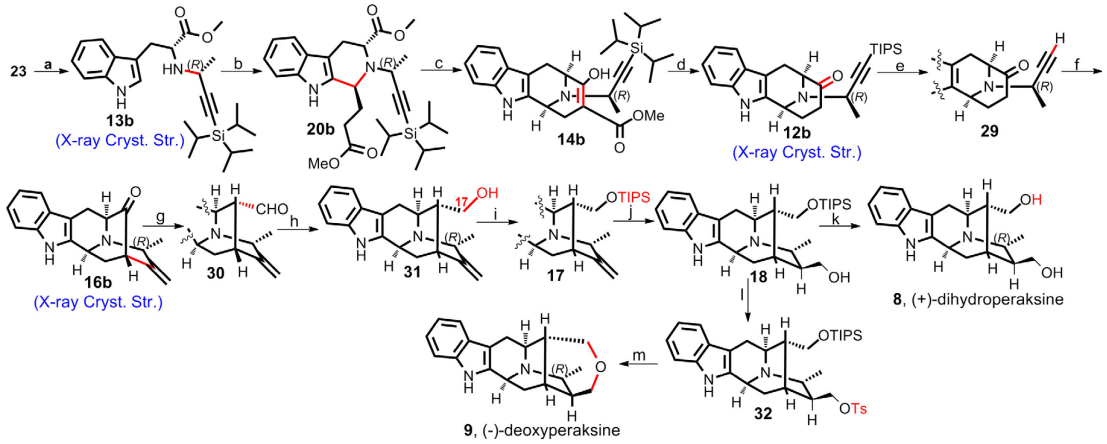
Retrosynthetically, the E-ring of the macroline system present in, for example, macrocarpines A–C (**1**–**3**) should originate in a stereocontrolled fashion from the Michael-type ring closure[11] of the deprotected alcohol on to the α,β-unsaturated aldehyde (**15**, Scheme 2), which in turn would be available from the pentacyclic ketone intermediates **16** [R = H or CH_3 and (*) = (*S*)], according to the previously reported route.[10,12] On the other hand, the C-19 α-methylated alkaloids dihydroperaksine **8** and deoxyperaksine **9** would be available from the TIPS-protected diol **18** which in turn would be available from **17** by a hydroboration-oxidation. The olefin **17** would be accessed from the ketone **16** [with R = H and (*) = (*R*)] in a few steps. The pentacyclic ketone intermediates **16** would be available by a copper-mediated intramolecular cross-coupling of the vinyl iodides **19** with the enolate.[12] The vinyl iodides (**19**) would be available from the TIPS-deprotected terminal alkyne by a completely regioselective iodoboration, after the decarboxylation of the β-ketoester **14**. The *trans*-diester **20** would originate as a sole product from the asymmetric Pictet–Spengler reaction of the N_b-alkylated tryptophan derivative **13** with the acetal **21** under thermodynamic control. Under these conditions the total synthesis would begin from commercially available D-tryptophan methyl ester **23** and the optically pure ethinyl tosylates (see **22**).

According to the plan, The N_b-nitrogen atom was alkylated with the optically pure TIPS protected tosylate units **22a** or **22b**, to introduce the ethinyl functions into indoles **13a** (Scheme 3) and **13b** (Scheme 4), respectively. The tosylate units were synthesized from the corresponding ketone (see the Supporting Information for details) by a ruthenium-catalyzed Noyori asymmetric hydrogenation,[13] followed by tosylation of the alcohol with TsCl. Reaction of the tosylate units **22a**/**22b** with the amine **23** in the presence of K_2CO_3 in CH_3CN furnished the S_N2 substituted products **13a** or **13b** (individually) in high yield, respectively. The structures and stereochemistry of **13a** and **13b** were confirmed by X-ray analysis (see the Supporting Information for X-ray data).

When **13a** was reacted with the actetal **21** under the thermodynamic conditions of the Pictet–Spengler reaction developed previously,[9b] the *trans*-diester was obtained in >95:5 diastereoselectivity (see the Supporting Information, Table S-1, entry 1). After initial success of the Pictet–Spengler reaction with the β-methyl [i.e., (*S*)] function **13a**, the same reaction conditions were then applied to the α-methyl [i.e., (*R*)] version **13b**, but this process resulted in incomplete reaction and complex reaction mixtures (Table S-1, entry 5). At that point, a modified method was required to reduce the reaction time in the case of the α-methyl compound **13b** to obtain conversion before decomposition. The use of a weaker acid (acetic acid) than TFA or a stronger acid (methanesulfonic acid) were not successful (Table S-1, entries 2–4, 6). The lack of conversion was, presumably, due to the low acidity of acetic acid and low reactivity of the acetal **21** whereas, $MeSO_3H$ was too acidic. However, when the acetal **21** was replaced by the aldehyde **27**, which was freshly prepared by the hydrolysis of the acetal **21**, and this mixture was stirred with the amine and acetic acid in DCM at room temperature, this gave the *cis*-diester as the



Scheme 3. Reagents and conditions: a) **22a** (1.5 equiv), K_2CO_3 (2.5 equiv), CH_3CN, 65 °C, 12 h, 85%; b) **21** (1.5 equiv), TFA (2.5 equiv), CH_2Cl_2, 11 d, *dr* = > 95:5, 89%; c) NaH (1.1 equiv), CH_3I (1.1 equiv), DMF, −10 °C to 0 °C, 3 h, 96%; d) NaH (3 equiv), MeOH (6 equiv), toluene, 110 °C, 8 h, 80%; e) CH_3COOH (glacial), HCl (conc.), H_2O, 110–130 °C, 7 h, 82%; f) TBAF (1.5 equiv), THF, 0 °C–rt, 3 h, 90%; g) see ref. [12]; h) see ref. [10]; i) NaHMDS (2 equiv), THF, rt, 12 h, 81%; j) i: 0.1 *N* aq. HCl, THF, reflux, 3 h, ii: *t*BuOK (2 equiv), THF, rt, 10 h, 84%; k) $NaBH_4$ (1.5 equiv), EtOH, 0 °C, 5 h, 99%; l) Ac_2O (1.5 equiv), Py (3 equiv), CH_2Cl_2, rt, 6 h, 92%; m) 0.1 *N* aq. HCl, THF, reflux, 3 h, 85%; n) $NaBH_4$ (1.5 equiv), EtOH, 0 °C, 5 h, 99%; o) *t*BuOK (2 equiv), THF, rt, 10 h, 82%.



Scheme 4. Reagents and conditions: a) **22b** (1.5 equiv), K_2CO_3 (2.5 equiv), MeCN, 65 °C, 12 h, 92%; b) $OHC(CH_2)_2CO_2Me$ (**27**, 1.5 equiv), acetic acid (2.5 equiv), rt, 70 h, 95%; c) NaH (9 equiv), MeOH (18 equiv), toluene, 110 °C, 72 h; d) HOAc (glacial), HCl (conc), H_2O, reflux, 36 h, 75% in 2 steps; e) TBAF (1.5 equiv), THF, 0 °C, 90%; f) see ref. [12]; g) $Ph_3P(Cl)CH_2OCH_3$, *t*BuOK, benzene, rt, 13 h, 2 *N* aq. HCl, THF, 55 °C, 6 h, 80% in 2 steps; h) $NaBH_4$, EtOH, 0 °C, 3 h, 90%; i) 2,6-lutidine, TIPS-OTf, 0 °C to rt, 2 h, 92%; j) 1. BH_3·DMS, THF, rt 2 h; $NaBO_3$·4 H_2O, 2 h, 2. Na_2CO_3, MeOH, reflux, 5 h, 76% over 2 steps; k) HF (aq), CH_3CN, 0 °C, 40 min, 89%; l) TsCl, Et_3N, DMAP, DCM, 2 h, 85%; m) TBAF, THF, −30 °C to rt, 1 h, 82%.

major product (*cis*:*trans* = 70: 30) and in overall 95% isolated yield (Table S-1, entry 8). Both the *cis*- and *trans*-diesters could easily be purified by chromtography and their stereochemistry was confirmed by NOE analysis. Importantly, the isolated *cis*-diester could be converted into the *trans*-diester with 100% diastereoselectivity on treatment with TFA in DCM at room temperature (Table S-1, entries 9, 11). If the *cis*-compound was stirred in acetic acid, the stereochemistry of these diastereomers (**28a** or **28b**) remained unchanged (see the Supporting Information, Table S-1, entries 10, 12). Nevertheless, having the *trans*-diester with both α- and β-methyl functions in hand, with 100% diastereoselectivity, was key to test the feasibility of this synthetic strategy.

The N_b- alkylated intermediate **13a** reacted with the actetal **21** under the thermodynamically controlled conditions of the asymmetric Pictet–Spengler condensation to furnish the desired *trans*-diester **20a** in excellent yield (Scheme 3). This *trans*-transfer of chirality set the required (*S*) stereochemistry at C-3 of the macroline-sarpagine related alkaloids. Methylation of the indole nitrogen with iodomethane in the presence of sodium hydride in DMF at 0 °C, yielded the N_a-CH_3 intermediate **24** in 96% yield. Dieckmann cyclization of the *trans*-diester was found to be troublesome due to the steric congestion surrounding the 1,2,3,-trisubstituted tetrahydro-β-carboline system **24**. However, when 3 equivalents of NaOMe (produced in situ) was reacted with *trans*-diester **24** in pre-dried toluene

at reflux (DST), the Dieckmann cyclization proceeded smoothly to furnish the β-ketoester (**14a**) in 80% yield. Hydrolysis of the ester or deprotection of the TIPS group was not observed during the cyclization. This step was crucial for the success of this synthetic route. Subsequently, decarboxylation of the β-ketoester under acidic conditions furnished the N_b-ethinyl tethered tetracyclic ketone **12a** without deprotection of the TIPS function. This route provided an improved synthesis of this intermediate **12a** by successfully avoiding the initial benzylation/debenzylation steps and effectively shortened the route by at least two steps. The spectral properties of this intermediate **12a** and optical rotation were identical in all respects, to an authentic sample of **12a**, synthesized by the previously reported route. This was further confirmed by X-ray crystallography after the deprotection of the TIPS function (**25**) with TBAF in THF (90% yield). An ORTEP drawing of ketone **25** is included in Scheme 3.

After the successful access to ketone **25** by the new route, the key pentacyclic ketone intermediate **16a** was prepared from the terminal alkyne **25** by conversion into the vinyl iodide [see Scheme 2; **19a**, R = CH_3, (*) = (*S*)], followed by a copper-mediated enolate-driven cross-coupling process similar to that reported earlier.[12] The advanced intermediate, quaternary ammonium salt **26**, which was required for accessing the macroline system, was synthesized by the same procedure reported previously. A retro-Michael ring opening of the quaternary salt **26** by treatment with sodium hexamethyldisilazane in THF produced, stereospecifically, the α,β-unsaturated aldehyde **15a** similar to the earlier work of Le Quesne et al.[11] In the previous report, the geometry of the olefin was not determined. We have confirmed the geometry of the olefin to be (*Z*) by the NOE observed upon irradiation of the aldehyde hydrogen atom with the β-methyl group and vice versa, as shown in Scheme 3. Deprotection of the TIPS function under mildly acidic conditions and subsequent Michael reaction of the so formed alcohol onto the α,β-unsaturated aldehyde, formed the E-ring of the macroline type alkaloids in excellent yield. The stereochemistry of the C-19 methyl group was found to be exclusively the β-stereochemistry by NMR experiments, which gave (+)-*N*(4)-methyl-*N*(4),21-*seco*talpinine **5** (major) and (−)-talcarpine **4** (minor). Upon aqueous workup after deprotection of the TIPS group under mildly acidic conditions (0.1 *N* aq. HCl), and subsequent treatment with *t*BuOK in THF, (+)-*N*(4)-methyl-*N*(4),21-*seco*talpinine (**5**) was isolated as the exclusive product. This indicated the aldehyde at C-20 was in the thermodynamically more stable position in the α-configuration.

Both (−)-**4** and (+)-**5** could easily be separated by silica gel chromatography with 1–5% methanol in CH_2Cl_2 (saturated with NH_4OH). (−)-Talcarpine **4** could also be converted completely into (+)-**5** upon treatment with base (Et_3N or K_2CO_3 in MeOH or *t*BuOK in THF). The spectral properties of (−)-talcarpine **4** and (+)-*N*(4)-methyl-*N*(4),21-*seco*talpinine **5** were in excellent agreement with the corresponding natural products.[2] The optical rotation of (+)-**5** has been revised by a personal communication with Professor Toh-Seok Kam [original value[2]: $[\alpha]_D = +19$ ($CHCl_3$, *c* 0.45); revised value: 2017 $[\alpha]_D = +36$ ($CHCl_3$, *c* 0.33); synthetic sample in this report: $[\alpha]_D = +34.43$ ($CHCl_3$, *c* 0.61)].[14] The properties of synthetic sample (−)-**4** in this report are in excellent agreement with the ^1H and ^{13}C NMR spectra of natural (−)-**4**. The optical rotation found to be in agreement with the optical rotation reported by Kam et al, (see the Supporting Information for details).[2]

After obtaining the pure aldehydes (−)-**4** and (+)-**5**, completion of the total synthesis of (−)-macrocarpines A-C (**1**–**3**) was undertaken. Aldehyde (−)-**4** was reduced with sodium borohydride in ethanol to produce (−)-macrocarpine A **1** in 99% isolated yield (Scheme 3). The ^1H, ^{13}C, 2D NMR, UV and MS spectra of synthetic (−)-**1** were in excellent agreement with the reported material **1**, except for the optical rotation ($[\alpha]_D = +117$ ($CHCl_3$, *c* 0.11)].[2] The original optical rotation of (−)-**1** has been revised by a personal communication with Professor Toh-Seok Kam and was in complete accord with a recent natural sample of (−)-**1** [natural: $[\alpha]_D = -28$ ($CHCl_3$, *c* 0.25);[15] synthetic, this report: $[\alpha]_D = -28$ ($CHCl_3$, *c* 0.25)] and hence, the optical rotation of the synthetic (−)-macrocarpine A (**1**) and the natural product are in excellent agreement. Reduction of (+)-**5** with sodium borohydride in ethanol furnished the natural product (−)-macrocarpine B (**2**) and the spectral properties and optical rotation of which were again in agreement with the natural product. Acetylation of alcohol (−)-**2** with acetic anhydride and pyridine in DCM, produced (−)-macrocarpine C (**3**), the properties of which were also in excellent agreement with that of the natural alkaloid (−)-**3**.[2]

After the completion of the total synthesis of the C-19 β-methyl substituted macroline related alkaloids; **1**–**5**, the focus changed to the synthesis of C-19 α-methyl substituted sarpagine alkaloids (+)-dihydroperaksine **8**, and (−)-deoxyperaksine **9**. The *trans*-diester **20b** was accessed through the process described above (Scheme 4). Dieckmann cyclization of the *trans*-diester **20b**, which contained the α-methyl [(*R*)] function, in the presence of 9 equivalents of sodium hydride and excess methanol in toluene at reflux furnished the cyclized product, the desired β-ketoester **14b**, which upon subsequent acid mediated decarboxylation produced the ketone intermediate **12b** in excellent yield (Scheme 4).

The optical properties of this intermediate were found to be identical with an authentic sample synthesized by the previous approach.[12] The structure was further confirmed by X-ray crystallography. The pentacyclic key intermediate **16b** was accessed from alkyne **29** via the vinyl iodide **19b** (see Scheme 2) by the previously reported copper-mediated enolate-driven cross-coupling process[12] and its structure was also confirmed by X-ray analysis (see the Supporting Information for X-ray data).

With the ketone **16b** in hand, a one-carbon homologation of the ketone function was carried out by a Wittig olefination with $(Ph)_3P^+(Cl^-)CH_2OCH_3$ and potassium *tert*-butoxide in benzene-THF, which furnished a mixture of enol ethers (structures not shown). The mixture of enol ethers, upon acid mediated hydrolysis (2 *N* aq. HCl in THF) furnished the thermodynamically favored α-aldehyde **30** as the sole product. Reduction of the aldehyde **30** was performed with sodium borohydride in ethanol, to produce the primary alcohol **31** in 90% yield. The de-

sired product from the Wittig olefination and hydrolysis could be carried onto the reduction step without purification and the alcohol **31** was isolated in this one-pot process. The protection of the hydroxyl function at C-17 with a TIPS function (**17**) was effected with TIPS-trifluoromethane sulfonate in DCM with 2, 6-lutidine in 92% yield. Hydroboration with BH_3·DMS, followed by Kabalka oxidation with sodium perborate, was performed to access the primary alcohol from the olefin **17** and this produced the primary alcohol **18** in 76% yield as the exclusive product. The corresponding tertiary alcohol was not observed.

(+)-Dihydroperaksine **8** was prepared simply by removing the TIPS function from **18** with a source of fluoride anion. The TIPS-deprotection with TBAF proceeded smoothly and completely but the tetrabutylammonium salt could not be readily removed from the product. Aqueous extraction was avoided due to the very polar nature of the alkaloid, which would have resulted in partial loss of material. Consequently, it was decided to use an alternative fluoride source of Corey et al., aqueous hydrogen fluoride,[16] so that solvents and TIPS-F could be removed effectively, in vacuo. Accordingly, deprotection of the TIPS function in **18** with aqueous HF in CH_3CN was completed smoothly in 40 minutes at 0 °C and pure synthetic (+)-**8** could be isolated after chromatography in 89% yield (Scheme 4). The optical rotation and spectral data for this synthetic (+)-**8** were in complete agreement with the values in the literature.[6c]

To access the ether linkage present in (−)-deoxyperaksine **9**, the primary alcohol in **18** which remained, was activated by tosylation in **32** (Scheme 4). Tosylation was effected in excellent yield with tosyl chloride and DMAP in DCM in 2 hours. Upon TIPS-deprotection with TBAF in THF at −30 °C in 1 hour, the so-formed primary alcohol reacted with the tosyl group in situ to furnish the ether ring present in (−)-deoxyperaksine **9**. The ^{1}H and ^{13}C NMR spectral data of (−)-**9** were not found in the literature.[17] This report represents the first report of the ^{1}H, ^{13}C, 2D NMRs, IR and MS characterization of (−)-deoxyperaksine **9**.

In summary, the first total synthesis of sarpagine/macroline related alkaloids have been completed through the shorter and expanded Pictet–Spengler reaction. The reported strategy has been illustrated to efficiently access alkaloids with both the α and β C-19 methyl function with 100% diastereoselectivity. This report also corrects the optical rotation values of (−)-macrocarpine A (**1**) and (+)-*N*(4)-methy, *N*(4), 21-*seco*talpinine (**5**) reported by others.[2] The optical rotation of (−)-talcarpine **4** was found to be in agreement with one of the two different optical rotations present in literature.[2,3c] This work clearly indicates that a large group other than benzyl on the N_b-nitrogen atom of the D-(+)-tryptophan starting material can still provide 100% diastereoselectivity by internal asymmetric induction. It is important to note that use of L-(−)-tryptophan would have provided the enantiomers of these alkaloids for biological study. In addition, the syntheses described here have extended the use of CuI-mediated enolate-driven cross-coupling reactions to a new system. This general strategy will be useful to access any member of C-19 methyl-substituted sarpagine/macroline alkaloids that are potential drug candidates, as indicated by their reported biological activities and presented in the introduction.

Acknowledgements

The authors wish to thank Professor Kam for helpful discussions as well as NIH grants NS076517 and MH096463 for generous financial support. The authors also thank the Shimadzu Analytical Laboratory of Southeastern Wisconsin for mass spectroscopy. G.H.I. acknowledges the American Society for Engineering Education (ASEE) for a postdoctoral fellowship.

Conflict of interest

The authors declare no conflict of interest.

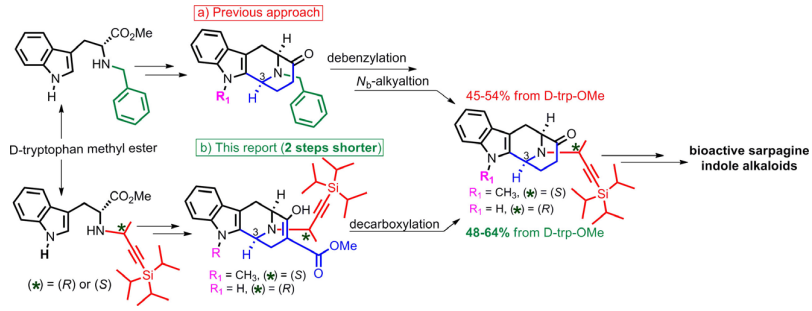
Keywords: enantiospecific · diastereospecific · indole alkaloids · Pictet–Spengler reaction · total synthesis

[1] T. Schmeller, M. Wink, in *Alkaloids: Biochemistry Ecology, and Medicinal Applications* (Eds.: M. F. Roberts, M. Wink), Springer US, Boston, MA, **1998**, pp. 435 – 459.
[2] T.-S. Kam, Y.-M. Choo, K. Komiyama, *Tetrahedron* **2004**, *60*, 3957 – 3966.
[3] a) N. Keawpradub, G. Kirby, J. Steele, P. Houghton, *Planta Med.* **1999**, *65*, 690 – 694; b) J. Naranjo, M. Pinar, M. Hesse, H. Schmid, *Helv. Chim. Acta* **1972**, *55*, 752 – 771; c) W.-H. Wong, P.-B. Lim, C.-H. Chuah, *Phytochemistry* **1996**, *41*, 313 – 315.
[4] L. Pan, C. Terrazas, U. M. Acuña, T. N. Ninh, H. Chai, E. J. C. de Blanco, D. D. Soejarto, A. R. Satoskar, A. D. Kinghorn, *Phytochem. Lett.* **2014**, *10*, 54 – 59.
[5] S.-J. Tan, J.-L. Lim, Y.-Y. Low, K.-S. Sim, S.-H. Lim, T.-S. Kam, *J. Nat. Prod.* **2014**, *77*, 2068 – 2080.
[6] a) J. Buckingham, K. H. Baggaley, A. D. Roberts, L. F. Szabo, *Dictionary of Alkaloids, with CD-ROM*, CRC press, **2010**; b) M. Iwu, *Planta Med.* **1982**, *45*, 105 – 111; c) A. Kiang, S. Loh, M. Demanczyk, C. Gemenden, G. Papariello, W. Taylor, *Tetrahedron* **1966**, *22*, 3293 – 3300; d) A. M. Nasser, W. E. Court, *Phytochemistry* **1983**, *22*, 2297 – 2300.
[7] a) J. Stöckigt, A. P. Antonchick, F. Wu, H. Waldmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 8538 – 8564; *Angew. Chem.* **2011**, *123*, 8692 – 8719; b) E. D. Cox, J. M. Cook, *Chem. Rev.* **1995**, *95*, 1797 – 1842; c) J. P. Mayer, D. Bankaitis-Davis, J. Zhang, G. Beaton, K. Bjergarde, C. M. Andersen, B. A. Goodman, C. J. Herrera, *Tetrahedron Lett.* **1996**, *37*, 5633 – 5636; d) L. Weber, *Curr. Med. Chem.* **2002**, *9*, 2085 – 2093.
[8] a) R. S. Klausen, E. N. Jacobsen, *Org. Lett.* **2009**, *11*, 887 – 890; b) P. D. Bailey, S. P. Hollinshead, N. R. McLay, *Tetrahedron Lett.* **1987**, *28*, 5177 – 5180; c) M. T. Rahman, V. V. Tiruveedhula, J. M. Cook, *Molecules* **2016**, *21*, 1525; d) R. Tsuji, M. Nakagawa, A. Nishida, *Tetrahedron: Asymmetry* **2003**, *14*, 177 – 180; e) T. Kawate, M. Yamanaka, M. Nakagawa, *Heterocycles* **1999**, *2*, 1033 – 1039; f) B. Herlé, M. J. Wanner, J. H. van Maarseveen, H. Hiemstra, *J. Org. Chem.* **2011**, *76*, 8907 – 8912; g) N. V. Sewgobind, M. J. Wanner, S. Ingemann, R. de Gelder, J. H. van Maarseveen, H. Hiemstra, *J. Org. Chem.* **2008**, *73*, 6405 – 6408; h) J. Seayad, A. M. Seayad, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 1086 – 1087.
[9] a) K. M. Czerwinski, J. M. Cook, *Stereochemical control of the Pictet-Spengler reaction in the synthesis of natural products, Vol. 3*, JAI Press: Greenwich, CT, **1996**; b) J. Li, T. Wang, P. Yu, A. Peterson, R. Weber, D. Soerens, D. Grubisha, D. Bennett, J. Cook, *J. Am. Chem. Soc.* **1999**, *121*, 6998 – 7010.
[10] R. V. Edwankar, C. R. Edwankar, J. R. Deschamps, J. M. Cook, *J. Org. Chem.* **2014**, *79*, 10030 – 10048.
[11] R. L. Garnick, P. W. Le Quesne, *J. Am. Chem. Soc.* **1978**, *100*, 4213 – 4219.
[12] M. T. Rahman, J. R. Deschamps, G. H. Imler, A. W. Schwabacher, J. M. Cook, *Org. Lett.* **2016**, *18*, 4174 – 4177.

[13] a) K. Matsumura, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 8738 – 8739; b) J. A. Marshall, P. Eidam, H. S. Eidam, *Org. Synth.* **2007**, 120 – 128.
[14] T. S. Kam, personal communication, July 12, **2017**. Revised optical rotation of *N*(4)-methyl-*N*(4),21-*seco*talpinine is: $[\alpha]_D = +36$ ($CHCl_3$, c 0.33).
[15] T. S. Kam, Personal Communication. April 09, **2016**. Updated values for macrocarpine A: see Ref. [2], $[\alpha]_D = -22$ (c 0.36, $CHCl_3$); unpublished results, $[\alpha]_D = -28$ (c 0.25, $CHCl_3$).
[16] E. Corey, Y. J. Wu, *J. Am. Chem. Soc.* **1993**, *115*, 8871 – 8872.
[17] M. Lounasmaa, P. Hanhinen, M. Westersund, in *The Alkaloids: Chemistry and Biology, Vol. 52* (Ed.: G. A. Cordell), Academic Press, San Diego, CA, **1999**, pp. 103 – 195.

Manuscript received: November 23, 2017
Accepted manuscript online: December 15, 2017
Version of record online: ■■ ■■, 0000

COMMUNICATION



Indole synthesis: We have extended the asymmetric Pictet–Spengler reaction to bulkier tryptophan derivatives. This resulted in an improved stereospecific access to the key bicyclo[3.3.1]nonane core of bioactive C-19 methyl substituted sarpagine/macroline/ajmaline indole alkaloids with excellent diastereoselectivity by internal asymmetric induction.

Bioactive Compounds

*M. T. Rahman, J. R. Deschamps, G. H. Imler, J. M. Cook**

■■ – ■■

Total Synthesis of Sarpagine-Related Bioactive Indole Alkaloids