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General approach for the total synthesis of the sarpagine related indole alkaloids (+)-N_a-methyl-16-epipericyclivine, (−)-alkaloid Q_3 and (−)-panarine via the asymmetric Pictet–Spengler reaction

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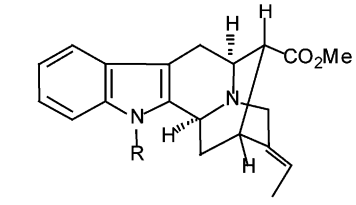
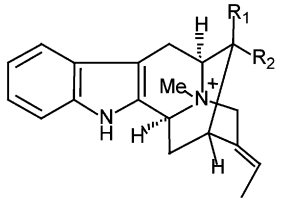
Abstract—The stereospecific total synthesis of (+)-N_a-methyl-16-epipericyclivine (**1**) was completed [from D-(+)-tryptophan methyl ester] in an overall yield of 42% (eight reaction vessels). The optical rotation {$[\alpha]_D$ +22.8 (*c* 0.50, $CHCl_3$)} obtained on this material confirmed that the reported optical rotation {$[\alpha]_D$ 0 (*c* 0.50, $CHCl_3$)} was biogenetically unreasonable. The first total synthesis of (−)-alkaloid Q_3 (**5**) and (−)-panarine (**6**), via the intermediate vellosimine (**18**), is also described.

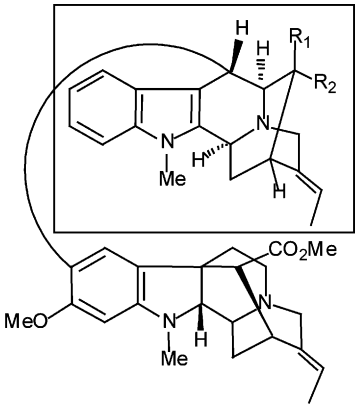
During the past few decades more than 90 sarpagine/macroline-related indole alkaloids have been isolated from *Alstonia macrophylla* Wall, *Alstonia muelleriana* Domin, and other *Alstonia* species.[1–3] Some of them have been used in traditional medicine as remedies for malaria and other ailments including tumors.[4,5] Surprisingly, only a few *Alstonia* alkaloids have been evaluated for biological activity due to the paucity of isolable material.[6–8] It has become apparent recently[7,9,10] that further work on the biological and chemical constituents of these medicinal plants is warranted. Among these bases, a few sarpagine-related monomeric alkaloids such as N_a-methyl-16-epipericyclivine (**1**)[11] and bisindole alkaloids such as desformoundulatine (**3**)[12]



1 R = CH_3, N_a-methyl-16-epipericyclivine
2 R = H, 16-epipericyclivine



5 R_1 = H, R_2 = CO_2Me, alkaloid Q_3
6 R_1 = H, R_2 = CO_2^-, panarine
7 R_1 = CO_2^-, R_2 = H, 16-epipanarine
8 R_1 = CO_2Me, R_2 = H



3 R_1 = CO_2Me, R_2 = H
4 R_1 = H, R_2 = CO_2Me

Figure 1.

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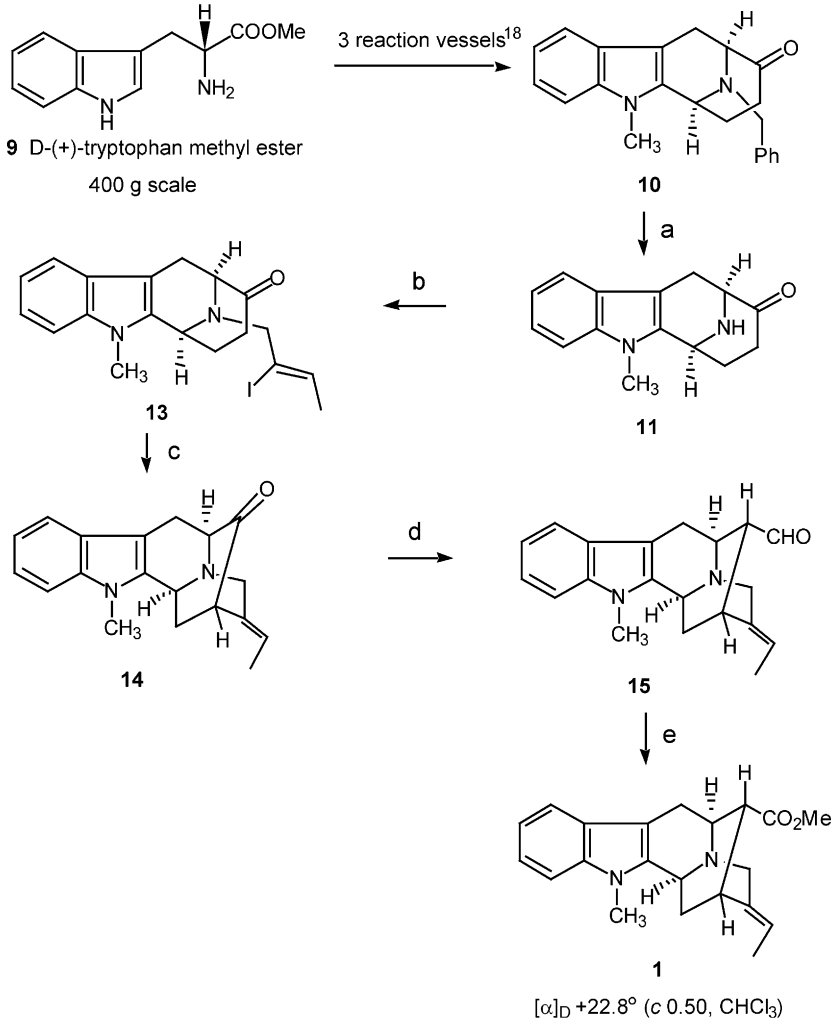
(from *Alstonia undulata*), form a subgroup of alkaloids which contain a methyl ester function at C-16 (Fig. 1). Bisindole alkaloids have been shown to exhibit antimalarial activity against a drug resistant (K-1) strain of *Plasmodia falciparum*[7,10] and dimeric alkaloids are usually much more potent than the monomeric units which comprise them against *P. falciparum* malaria.[6–8] It was therefore of interest to synthesize and evaluate these bisindole alkaloids. It has previously been demonstrated by Le Men-Olivier et al.[13] that natural N_a-methyl-16-epipericyclivine (**1**) couples with the natural monomeric alkaloid cabucraline to provide bisindole **4** on treatment with DDQ. Interestingly, the optical rotation of **1** was reported as zero,[11] which was biogenetically unreasonable. As a consequence, the total synthesis of **1** and eventually bisindoles **3** and **4** has become of interest. Potential new drug candidates could emerge from these bisindoles and material is required to study the mechanism of action at the cellular level.

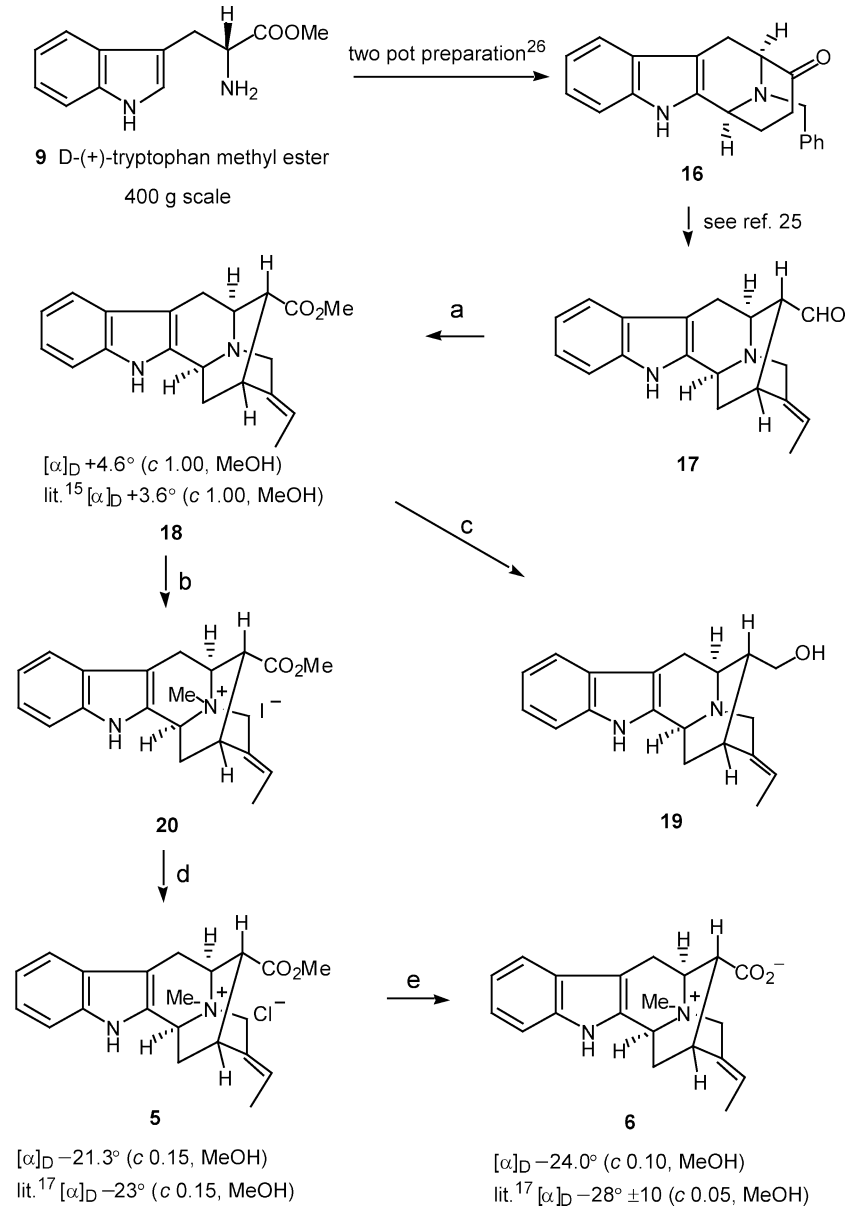
Quaisuddin[14] in 1980 isolated a quaternary alkaloid **5** from *Aspidosperma perba* which was designated as alkaloid Q_3. Based on chemical transformations, alkaloid Q_3 (**5**) was converted into 16-epipericyclivine (**2**), a material which had not yet been isolated as a natural product. However, the optical rotation of **2** reported by Quaisuddin[14] {$[\alpha]_D$ +37.7 (*c* 0.13, MeOH)} was not consistent with that reported by Büchi et al.[15] {$[\alpha]_D$ +3.6 (*c* 1.00, MeOH)}. Furthermore, because only a few physical properties were reported, the identity of alkaloid Q_3 could not be established unambiguously. Angenot et al.[16] in 1988 isolated two closely related quaternary alkaloids including panarine (**6**) from a Venezuelan curare. This material was prepared by the Panare Indians from the bark of *Strychnos toxifera* Rob. Schomb. Ex Lindley. Its structure has been established unequivocally by ^1H and ^{13}C NMR spectra and X-ray crystallographic analysis.[16] Another related quaternary alkaloid 16-epipanarine (**7**) was isolated from *Stemmadenia minima* in 1991 by Achenbach et al.[17] In order to directly compare an authentic sample of **7** with **6** and establish the correct configuration of **7**, chemical correlations were carried out. The three steps included esterification with thionyl chloride in methanol to



Scheme 1. *Reagents and conditions*: (a) 5% Pd/C, H_2, EtOH/HCl, rt, 5 h, 94%; (b) *Z*-1-bromo-2-iodo-2-butene **12**, K_2CO_3, THF, reflux, 90%; (c) 3 mol% $Pd(OAc)_2$, 30 mol% PPh_3, 1 equiv. Bu_4NBr, 4 equiv. K_2CO_3, DMF–H_2O (9:1), 65°C, 30 h, 82%; (d) $MeOCH_2PPh_3Cl$, KOt-Bu, benzene, rt, 24 h; 2N HCl/THF, 55°C, 5 h, 90%; (e) KOH, I_2, MeOH, rt, 2 h, 94%.

provide **8**, epimerization on treatment of **8** with potassium *t*-butanolate to obtain **5**, and alkaline hydrolysis of **5** to afford **6** as the only product.[17] However, no report of the total synthesis of these quaternary alkaloids has appeared in the literature, to date, and the reported[11] rotation of **1** was in question.

The synthesis of **1** began from N_a-methyl, N_b-benzyl tetracyclic ketone **10** which could be prepared on 150 g scale (>98% ee) from D-(+)tryptophan methyl ester in three reaction vessels via the asymmetric Pictet–Spengler reaction/Dieckmann protocol (Scheme 1).[18] The N_b-benzyl group was removed via catalytic hydrogenation to afford the N_b-H ketone **11** in 94% yield. This base was reacted with the *Z*-1-bromo-2-iodo-2-butene **12** in the presence of K_2CO_3 to afford alkylated ketone **13** in 90% yield. Palladium-mediated enolate driven intramolecular cyclization took place stereospecifically to afford the desired ketone **14** in 82% yield.[19] Ketone **14** was then converted into N_a-methylvellosimine (**15**) which had also been isolated from *Rauvolfia nitida*.[20] The total synthesis of **15** had not been previously reported.[21] Oxidation of the C-17 aldehyde function of **15** to the desired ester afforded N_a-methyl-16-epipericyclivine (**1**)[22] in 94% yield on treatment with I_2 and KOH in MeOH.[23,24] This sequence provided stereospecific access to (+)-N_a-methyl-16-epipericyclivine (**1**) in eight reaction vessels (42% overall yield). All spectral data (e.g. ^{1}H and ^{13}C NMR, IR, and MS) for synthetic **1** were in good agreement with data reported for the natural product.[11] However, the optical rotation of synthetic N_a-methyl-16-epipericyclivine (**1**) {$[\alpha]_D$ +22.8 (*c* 0.50, $CHCl_3$)} was different from that reported {$[\alpha]_D$ 0 (*c* 0.50, $CHCl_3$)}.[11]



Scheme 2. *Reagents and conditions*: (a) KOH, I_2, MeOH, rt, 2 h, 88%; (b) $LiAlH_4$, THF, reflux, 2 h, 92%; (c) MeI, MeOH, rt, 4 h, 90%; (d) AgCl, MeOH, 85%; (e) 0.1N NaOH, then 0.1N HCl, 90%.

As shown in Scheme 2, vellosimine (**17**) was chosen as an important intermediate for the total synthesis of (−)-alkaloid Q_3 (**5**) and (−)-panarine (**6**). Tao et al.[25] reported a concise and efficient synthesis of vellosimine (**17**) which provided gram quantities of this alkaloid. Consequently, D-(+)tryptophan methyl ester (**9**) was converted into the N_a-H, N_b-benzyl tetracyclic ketone **16** via a two vessel process.[26] Tetracyclic ketone **16** was transformed into the desired vellosimine (**17**) stereospecifically in five steps. Oxidation of the aldehyde **17** at C-17 to provide the ester **18** was best accomplished in 85% yield again by using I_2 and KOH in MeOH. The optical rotation of synthetic **18** {$[\alpha]_D$ +4.6 (*c* 1.00, MeOH)} was in agreement with that of Büchi and not of Quaisuddin.[14,15] Since the absolute configuration of normacusine B (**19**) was known, the ester in **18** was reduced with $LiAlH_4$ to give the monol **19** in 92% yield. The spectroscopic and physical data {^1H and ^{13}C NMR, IR, and $[\alpha]_D$} of normacusine B (**19**) were identical in all respects with the published data,[15,27–29] which confirmed the correct configuration of **19** and **18** (vide infra) as well. Subsequent quarternization of the N_b-nitrogen moiety in **18** with MeI provided the N_b-methiodide salt **20** which was, upon exposure to AgCl,[30] converted into the chloride **5** in 85% yield. The ^1H NMR spectrum and optical rotation of **5** are in good agreement with that of the reported values.[17] Hydrolysis of the ester function of **5** with 0.1N NaOH, followed by neutralization with 0.1 HCl afforded (−)-panarine (**6**) in 90% yield.[31] The ^1H and ^{13}C NMR spectra of synthetic **6** were identical to that of natural panarine kindly supplied by Professor Luc Angenot. Moreover, a mixed sample (1:1) of synthetic (−)-panarine and natural (−)-panarine yielded only one set of signals in the ^{13}C NMR. The two compounds are identical.

In summary, the concise synthesis of (+)-N_a-methyl-16-epipericyclivine (**1**) was completed in stereospecific, enantiospecific fashion in 42% overall yield in eight reaction vessels. The optical rotation {$[\alpha]_D$ +22.8 (*c* 0.50, $CHCl_3$)} of synthetic material (>98% ee) indicated that the reported optical rotation {$[\alpha]_D$ 0 (*c* 0.50, $CHCl_3$)} was biogenetically unreasonable. In addition, this (+)-N_a-methyl-16-epipericyclivine (**1**) could be employed to prepare the bisindole alkaloid **4** analogous to the earlier work of Le Men-Olivier et al.[11] Studies on the total synthesis of bisindoles **3** and **4** are currently underway in our laboratory. The first total synthesis of the two quaternary alkaloids, (−)-alkaloid Q_3 (**5**) and (−)-panarine (**6**), was also accomplished via the important intermediate, vellosimine (**17**), which had recently been synthesized in Milwaukee.

Acknowledgements

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22. N_a-Methyl-16-epipericyclivine (**1**): $[\alpha]_D = +22.8°$ (*c* 0.50, $CHCl_3$), lit.[11] $[\alpha]_D = 0°$ (*c* 0.50, $CHCl_3$). IR (KBr) 1730, 1470 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.64 (3H, dt, $J = 6.8$, 1.9 Hz), 1.76 (1H, ddd, $J = 12.6$, 2.6, 1.4 Hz), 2.18 (1H, ddd, $J = 12.2$, 10.0, 1.9 Hz), 2.61 (1H, dd, $J = 7.8$, 1.4 Hz), 2.74 (1H, dd, $J = 15.8$, 1.0 Hz), 3.25 (2H, m), 3.61 (3H, s), 3.70 (3H, s), 3.76 (3H, m), 4.40 (1H, d, $J = 9.1$ Hz), 5.42 (1H, q, $J = 6.7$ Hz), 7.11 (1H, ddd, $J = 8.9$, 7.9,

1.2 Hz), 7.23 (1H, td, $J=6.9$, 1.2 Hz), 7.29 (1H, d, $J=7.7$ Hz), 7.50 (1H, d, $J=7.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.69, 26.80, 28.28, 29.30, 32.11, 46.50, 48.98, 51.74, 53.00, 55.82, 103.10, 108.82, 117.89, 118.22, 119.03, 121.21, 126.99, 132.67, 137.36, 137.88, 173.39. EIMS (m/z, relative intensity) 336 (M^+, 82), 277 (21), 241 (21), 182 (100), 168 (36). Anal. calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.72; H, 6.85; N, 7.97.

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31. Synthetic panarine (**6**): $[\alpha]_D=-24.0°$ (c 0.10, MeOH), lit.[17] $[\alpha]_D=-28°\pm10$ (c 0.05, MeOH). IR (KBr) 1738 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.53 (3H, d, $J=6.7$ Hz), 2.07 (1H, dd, $J=13.2$, 3.8 Hz), 2.43 (1H, t, $J=12.3$ Hz), 2.51 (1H, d, $J=7.6$ Hz), 2.88 (1H, d, $J=17.3$ Hz), 3.03 (3H, s), 3.24 (1H, dd, $J=17.3$, 5.0 Hz), 3.36 (1H, br s), 4.11 (1H, d, $J=15.4$ Hz), 4.16 (1H, t, $J=6.4$ Hz), 4.28 (1H, d, $J=15.4$ Hz), 4.80 (1H, d, $J=5.0$ Hz), 5.47 (1H, q, $J=6.7$ Hz), 7.11 (1H, t, $J=7.3$ Hz), 7.22 (1H, t, $J=7.1$ Hz), 7.43 (1H, d, $J=8.1$ Hz), 7.51 (1H, d, $J=7.9$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.06, 23.41, 28.21, 31.03, 47.13, 49.03, 60.18, 64.23, 64.69, 100.84, 111.86, 118.39, 119.93, 120.70, 122.74, 125.61, 126.61, 131.59, 136.67, 176.95. EIMS (m/z, relative intensity) 336 [$(M+Me)^+$, 8], 322 (M^+, 81), 307 (47), 291(7), 278 (21), 263 (79), 249 (32), 247 (41), 169 (87), 168 (100).