Total Synthesis

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Enantioselective Total Synthesis of (−)-Terengganensine A

*Cyril Piemontesi, Qian Wang, and Jieping Zhu**

Abstract: *A seven-step enantioselective total synthesis of (−)-terengganensine A, a complex heptacyclic monoterpene indole alkaloid, was accomplished. Key steps included: a) Noyori's catalytic enantioselective transfer hydrogenation of the iminium salt to set up the absolute configuration at the C21 position; b) a highly diastereoselective C7 benzoyloxylation with dibenzoyl peroxide under mild conditions; and c) an integrated one-pot oxidative cleavage of cyclopentene/triple cyclization/hydrolysis sequence for the construction of the dioxa azaadamantane motif with complete control of four newly generated stereocenters.*

The natural products (−)-terengganensine A (**1**) and terengganensine B (**2**) were isolated by Païs and co-workers in 1997 from the bark of *Kopsia terengganensis* (Figure 1).[1] This unprecedented heptacyclic compound contains six stereocenters and an unusual [5.6.6.6]azafenestrane system[2] embedded

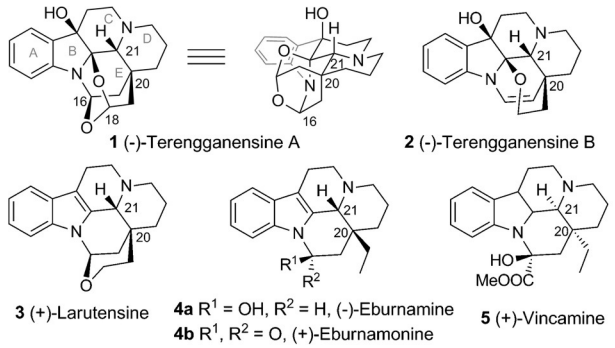
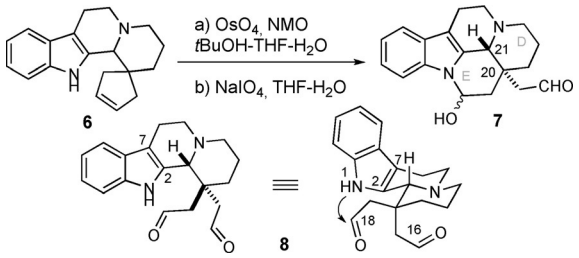


Figure 1. (−)-Terengganensine A (**1**) and related members of the family of eburnane alkaloids.

in a dioxa azaadamantane motif. Detailed NMR studies enabled the determination the relative stereochemistry of terengganensine A (**1**) and to conclude that the B, C, D, and E rings are all in chair conformations with the following ring-junction features: B–C (*cis*), C–D (*trans*), and D–E (*cis*). Since the known (+)-larutensine (**3**) and (−)-eburnamine (**4a**), whose absolute configurations at the C20 and C21 positions have previously been determined without ambiguity,[3] were co-isolated from the same plant, the absolute configurations of **1** and **2** were deduced by analogy as shown in Figure 1. We noted that plants derived from different regions are capable of producing levorotatory, dextrorotatory, and racemic forms of eburnane alkaloids. Even more relevantly, (±)-eburnamonine (*rac*-**4b**) has been isolated together with (−)-eburnamine (**4a**) from the very same plant *vinca minor L*.[4] Therefore to confirm the absolute configurations of these natural products, an enantioselective synthesis would be of high value.

The eburnane-vinca monoterpene indole alkaloids display potent bioactivities in the central nervous system (CNS). For example, (−)-eburnamonine (**4b**) has been shown to prevent cerebrovascular disorders, whereas (+)-vincamine (**5**; Oxybral SR) is a marketed peripheral vasodilator.[5] Many elegant total syntheses of eburnamine (**4a**), vincamine (**5**), and related natural products have been developed over the years.[6,7] However, no total synthesis of terengganensine A (**1**) has been reported to date. In their synthesis of (±)-eburnamonine (*rac*-**4b**), Ho and Chen reported a two-step conversion of **6** into pentacycle **7** with an undesired *trans*-fused D–E ring that was subsequently transformed, through a multistep sequence, to the *cis*-fused ring system found in the natural products (Scheme 1).[8] Although this paper did not



Scheme 1. The approach of Ho and Chen to the synthesis of (±)-eburnamine (*rac*-**4a**) and (±)-eburnamonine (*rac*-**4b**).[8] NMO = *N*-methylmorpholine *N*-oxide.

address the synthesis of terengganensine A, the diastereoselective cyclization of dialdehyde **8** to **7**, albeit with the incorrect selectivity, caught our attention. Reasoning that the C2=C7 double bond in **8** is responsible for the preferred attack of the indole nitrogen on the C20 equatorially positioned CH_2CHO functional group (C18),[9] we hypothesized that by converting the indole into the C7-β-hydroxylated indoline motif, the C20 axially positioned CH_2CHO group (C16) would be more accessible for the indoline nitrogen. Had this been the case, a domino cyclization could be expected leading eventually to terengganensine A (**1**) in a single operation.

Based on this assumption, a retrosynthetic analysis of **1** is shown in Scheme 2. Disconnection of the acetal and the two

[*] C. Piemontesi, Dr. Q. Wang, Prof. Dr. J. Zhu
Laboratory of Synthesis and Natural Products
Institute of Chemical Sciences and Engineering
Ecole Polytechnique Fédérale de Lausanne
EPFL-SB-ISIC-LSPN, BCH 5304, 1015 Lausanne (Switzerland)
E-mail: jieping.zhu@epfl.ch
Homepage: http://lspn.epfl.ch

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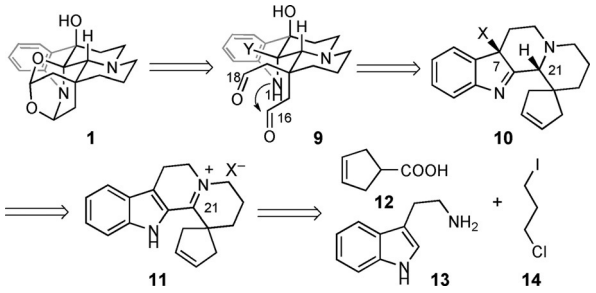
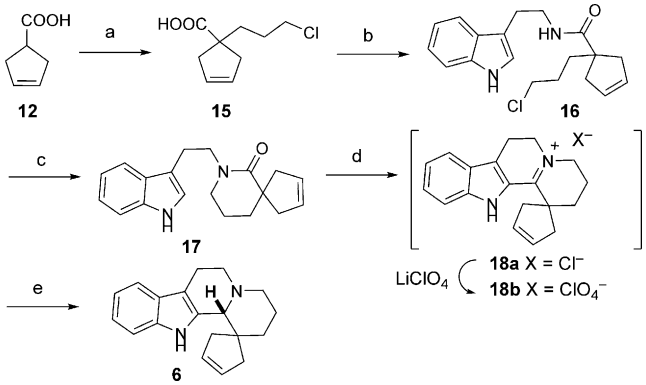


Scheme 2. Retrosynthetic analysis of (−)-terengganensine A (**1**).

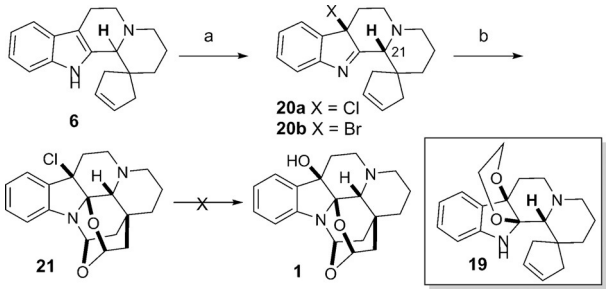
aminal functions in **1** would afford intermediate **9** which could be prepared from **11** via **10**. We thought to control the absolute configuration at the C21 position by catalytic enantioselective reduction of iminium salt **11**. The latter could in turn be synthesized from cyclopentene **12** and tryptamine (**13**), both being commercially available.

Our synthesis of pentacycle **6** is shown in Scheme 3. Double deprotonation of carboxylic acid **12** followed by addition of 1-chloro-3-iodopropane (**14**, 1.0 equiv) afforded chemoselectively the *C*-alkylated product **15** in 89% yield. Acyl chloride formation followed by amidation with tryptamine (**13**) converted **15** into **16**, which, without purification, was cyclized under basic conditions to spirolactam **17** (LHMDS, THF, −78 °C then RT). The Bischler–Napieralski reaction of the crude product **17** ($POCl_3$ in MeCN) provided a water-soluble chloride salt **18a**. To facilitate its purification, it was converted into perchlorate salt **18b** that can be extracted easily with an organic solvent. Reduction of **18b** with sodium borohydride furnished **6** in 56% overall yield from **15**. In this four-step sequence, only one column chromatographic purification of the final product **6** was needed. The sequence is much more efficient than that used by Ho and co-workers involving the Pictet–Spengler reaction as a key step.[8]



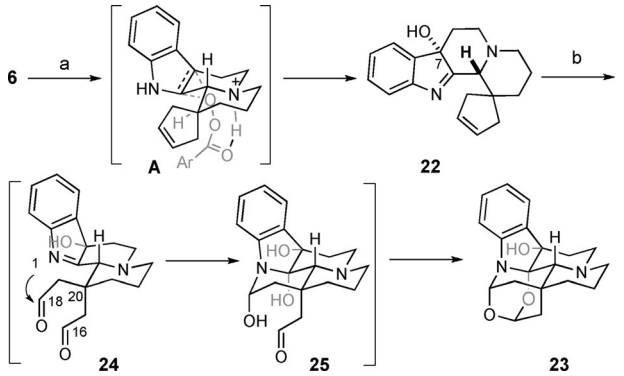
Scheme 3. Synthesis of pentacycle **6**: a) LDA (2.2 equiv), THF, −10 °C, then $ICH_2CH_2CH_2Cl$ (**14**), −10 °C to 0 °C, 89%; b) $(COCl)_2$, DMF, 0 °C to RT, then Et_3N, tryptamine (**13**), $CHCl_3$, 0 °C to RT; c) LHMDS, THF, −78 °C to RT; d) $POCl_3$, MeCN, 100 °C, then $LiClO_4$; e) $NaBH_4$, EtOH, 0 °C, 56% overall yield from **15**. LDA = lithium diisopropylamide; LHMDS = lithium hexamethyl disilazide.

Our initial attempt to convert the indole motif in **6** into 2,7-ethylene glycol bridged adduct **19** (phenyliodine(III) bistrifluoroacetate (PIFA), $HOCH_2CH_2OH$, NH_4Cl, MeCN, 0 °C) afforded only the C7-chlorinated product **20a** in a moderate yield.[10] Reasoning that **20a** could be an appropriate precursor for our designed domino cyclization, conditions for its production were further optimized. Among various conditions screened, reaction of **6** with *tert*-butyl hypochlorite afforded **20a** as a single diastereoisomer in 95% yield (Scheme 4).[11,12] The presence of Bohlman bands (2801, 2748 cm^{-1}) in the IR spectrum of **6** indicated that its C–D ring is *trans* fused, a fact that accounted for the observed β-selectivity in the C7 chlorination step.[13] Gratefully, the Upjohn dihydroxylation[14] of **20a** followed by addition of phenyliodine diacetate (PIDA)[15] afforded directly 7-deoxy-7-chloro-terengganensine A (**21**) as a single diastereomer in 89% yield. However, all efforts to perform the nucleophilic substitution of C7–Cl by oxygen-based nucleophiles failed to produce the natural product. We have also synthesized **20b** (X = Br) using *N*-bromosuccinimide (NBS) as the brominating agent. Unfortunately, attempts to perform the hydroxylation or acetoxylation of **20a** and **20b** under a variety of conditions met with failure.



Scheme 4. Synthesis of 7-deoxy-7-chloro-terengganensine A (**21**): a) For **20a**: *t*BuOCl, CH_2Cl_2, RT, 95%; For **20b**: NBS, acetone, RT, 78%; b) OsO_4 (0.02 equiv), NMO, 2,6-lutidine, Me_2CO-H_2O, RT, then PIDA, RT, 89%. NBS = *N*-bromosuccinimide.

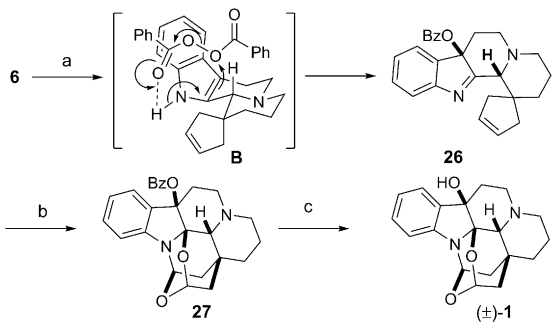
A direct C7 hydroxylation or acetoxylation of **6** was next investigated. The competitive oxidation of the tertiary amine to an *N*-oxide and the facile Wagner–Meerwein rearrangement of the resulting hydroxylated indolenine leading to oxindole complicated significantly the reaction outcome.[16] After having screened over fifty conditions, the desired transformation was finally realized with *meta*-chloroperbenzoic acid (*m*CPBA) in CH_2Cl_2 in the presence of an excess of trifluoroacetic acid (TFA) at −78 °C (Scheme 5).[17] Under these conditions, compound **22** was isolated in 95% yield as a single isomer. Although it is difficult to assign the stereochemistry at the C7 position with certainty, we observed that the ^1H NMR spectrum of **22** was significantly different from that of **20a** and **20b** (for details, see the Supporting Information) and tentatively concluded that the hydroxylation occurred from the sterically less accessible α-face of the C2=C7 double bond. Such unusual stereoselectivity could be explained by invoking the intermediate **A** in which a hydrogen-bonding interaction between the ammoni-



Scheme 5. C7-hydroxylation by *m*CPBA—an unexpected stereochemical outcome: a) *m*CPBA (1.0 equiv), TFA (17.0 equiv), CH_2Cl_2, −78 °C, 95 %; b) OsO_4 (0.02 equiv), NMO, 2,6-lutidine, Me_2CO-H_2O, RT, then PIDA, RT, 75 %.

um salt and *m*CPBA directed the reaction trajectory.[17] Subjecting **22** to the one-pot double bond cleavage/cyclization sequence established for the conversion of **20a** into **21** (see Scheme 4) provided heptacyclic compound **23** whose NMR spectra were significantly different from those of terengganensine A. We reasoned that, upon formation of dialdehyde **24**, the nitrogen N1 would attack, as a result of the geometric constraint, the C20 equatorially oriented CH_2CHO functional group (C18) leading to hemiaminal **25** that would further cyclize to heptacycle **23**. Since both hemiaminal and acetal formation is reversible and the configurations at the C2 and C7 positions in **23** are in principle adjustable under acidic conditions, compound **23** was subsequently treated with a diverse set of Lewis acids and Brønsted acids. However, only recovery or decomposition of the starting material was observed.

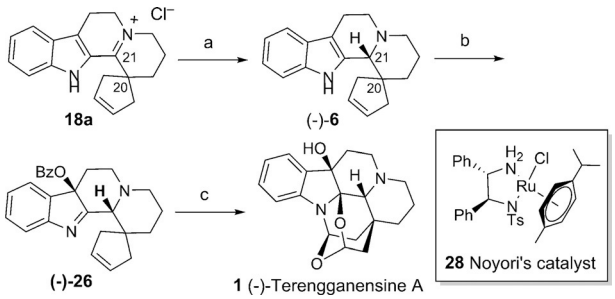
It became clear that in order to realize the total synthesis of terengganensine A (**1**), stereoselective introduction of a β-OH function at the C7 position is a prerequisite. After a survey of many different sets of reaction conditions, it was found that simply stirring a chloroform solution of **6** with dibenzoyl peroxide (DBP, 1.0 equiv) at RT afforded **26** in 68 % yield (Scheme 6).[18] Since DBP is stable at RT and our reaction worked with equal efficiency in the dark,[19] we



Scheme 6. Total synthesis of (±)-terengganensine A (*rac*-**1**): a) Bz_2O_2 (DBP), $CHCl_3$, RT, 68 %; b) OsO_4 (0.02 equiv), NMO, 2,6-lutidine, Me_2CO-H_2O, RT, then PIDA, RT, 76 %; c) 1.0 % NaOH, MeOH, 40 °C, 95 %.

hypothesized that the present benzoyloxylation proceeded most probably via an ionic rather than a radical pathway.[20] The reaction presumably went through intermediate **B** in which a hydrogen-bonding interaction between the indole NH and one of the carbonyl groups of the DBP would facilitate the cleavage of the peroxide bond. One-pot oxidation/cyclization of **26** under our established conditions furnished **27** (76 % yield), which, upon hydrolysis (NaOH, MeOH), afforded (±)-terengganensine A (*rac*-**1**) in 95 % yield. The last step can be integrated into the oxidation/cyclization sequence allowing a one-pot conversion of **26** into *rac*-**1** in 80 % yield.

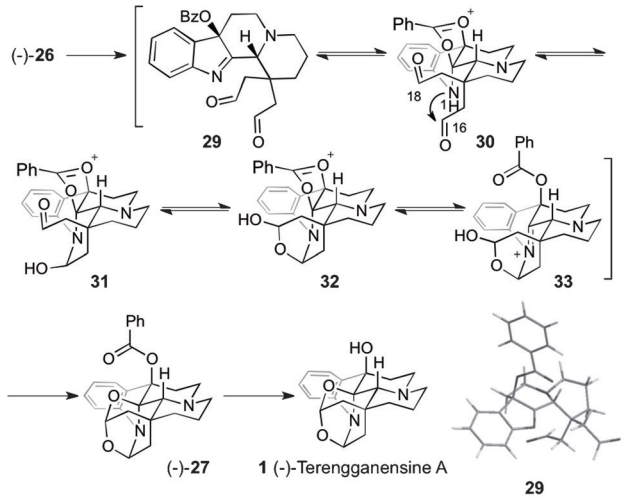
With these results in hand, an enantioselective synthesis of (−)-terengganensine A (**1**) was pursued (Scheme 7). Noyori's catalytic enantioselective transfer hydrogenation of iminium salt **18** was thought to be an ideal means to control the absolute configuration at the C21 position, although only very



Scheme 7. Enantioselective synthesis of (−)-terengganensine A (**1**): a) **28** (0.05 equiv), HCOONa (15.0 equiv), $AgSbF_6$ (0.3 equiv), CTAB (1.0 equiv), degassed water, 40 °C, 2 days, then introducing additional **28** (0.025 equiv), $AgSbF_6$ (0.15 equiv), 40 °C, 2 days, 70 % yield with 90 % *ee*; b) Bz_2O_2 (DBP), $CHCl_3$, RT, 76 %; c) OsO_4 (0.02 equiv), NMO, 2,6-lutidine, Me_2CO-H_2O, RT, then PIDA, RT, then 1.0 % NaOH, MeOH, 40 °C, 86 %. CTAB = Cetyltrimethylammonium bromide.

few examples are known in the literature.[21,22] The presence of a neighboring quaternary carbon (C20) rendered this reduction even more challenging. Initial screening of the reaction conditions indicated that reduction of the chloride salt **18a** gave in general higher enantioselectivity than that of the perchlorate salt **18b**. Under slightly modified Pihko's conditions[22a] using the Ru complex of (1*S*,2*S*)-*N*-tosyldiphenylethylenediamine (TsDPEN, **28**) as a pre-catalyst, we were able to convert **18a** into (−)-**6** in 70 % yield with 90 % *ee*. The absolute configuration at the C21 position was assigned as *R* according to literature precedents.[21,22] Diastereoselective C3 benzoyloxylation of (−)-**6** under our established conditions provided (−)-**26** that was transformed into (−)-terengganensine A (**1**) by an integrated one-pot oxidative cleavage of cyclopentene/cyclization/hydrolysis process. The physical and spectroscopic data of the synthetic (−)-terengganensine A (**1**) were identical to those reported for the natural product. The sign of $[\alpha]_D$ together with the NMR data allowed us to confirm the absolute configuration of terengganensine A (**1**) initially assigned by Païs and co-workers.[23]

A possible reaction pathway for the one-pot conversion of (−)-**26** into (−)-terengganensine A (**1**) is shown in Scheme 8.



Scheme 8. Possible reaction pathway for the integrated one-pot oxidation/cyclization/hydrolysis process and computed lowest energy conformation of **29**.

OsO_4-catalyzed dihydroxylation of cyclopentene followed by $PhI(OAc)_2$-mediated cleavage of the resulting diol would provide dialdehyde **29** that would spontaneously cyclize to form hemiaminal **31** via presumed intermediate **30**.[24] The lowest energy conformation computed for **29** (DFT geometry optimization was performed using Gaussian 09 at the B3LYP/6-31G + (d) level) indicated clearly that the neighboring benzoyl carbonyl group might assist in the aminal forming step (distance of O–C2 = 2.44 Å, Bürgi–Dunitz angle N-C-O = 107.2°). The stereochemistry at the C7 position determined the group selectivity of this cyclization and, in this case, only the C20 axial CH_2CHO group (C16) would be attacked by N1, therefore desymmetrizing selectively the C20 prochiral stereogenic center. Further cyclization of the resulting alcohol to the pendant aldehyde would afford hemiacetal **32** that would cyclize to (−)-**27** via **33**. Finally, hydrolysis of (−)-**27** afforded (−)-terengganensine A (−)-**1**.

In conclusion, the first enantioselective total synthesis of (−)-terengganensine A (**1**) has been accomplished in seven steps in the longest linear sequence from cyclopent-3-ene-1-carboxylic acid (**12**) with 23% overall yield. Key steps included a) Noyori's catalytic enantioselective transfer hydrogenation of an iminium salt to set up the absolute configuration at the C21 position; b) a highly diastereoselective C7 benzoyloxylation with dibenzoyl peroxide under mild conditions; and c) an integrated oxidative cleavage of cyclopentene/triple cyclization/hydrolysis for the construction of the dioxa azaadamantane motif with complete control of four newly generated stereogenic centers.

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Keywords: asymmetric synthesis · domino cyclization · hydroxylation · monoterpene indole alkaloids · total synthesis

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[12] The presence of the spirocyclopentene unit in **6** might also be responsible for the observed high diastereoselectivity. Chlorination of C20-unsubstituted octahydroindolo[2,3-*a*]quinolizine under similar conditions afforded a mixture of two diastereomers. See: L. J. Dolby, G. W. Gribble, *J. Org. Chem.* **1967**, *32*, 1391–1398.
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[18] Commerical DBP (Luperox A70S, 70% remainder water) was purified by dissolving the compound in $CHCl_3$ at 0°C and precipitated by adding an equal volume of methanol. The solid was dried under a flux of nitrogen followed by high vacuum for 24 h. See: W. L. F. Armarego, C. L. L. Chai, *Purification of Laboratory Chemicals* 5th ed., Butterworth-Heinemann, Elsevier, Burlington, **2003**, pp. 125 – 126. This compound can be stored for weeks in a freezer without noticeable degradation.
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