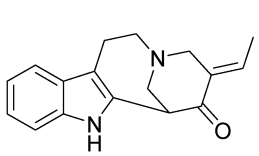
Total synthesis and absolute configuration determination of (+)-subincanadine F†

Pinhong Chen, Lidong Cao, Wenhai Tian, Xinfeng Wang and Chaozhong Li*

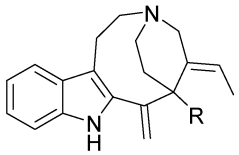
Received 24th August 2010, Accepted 15th September 2010
DOI: 10.1039/c0cc03428b

The first asymmetric synthesis of indole alkaloid (+)-subincanadine F was successfully accomplished with the uncommon 7-*endo*-trig stereoselective radical cyclization as the key step and its absolute configuration was thus assigned.

Bridged, medium-sized nitrogen heterocycles are embedded in a number of indole alkaloids such as subincanadines F (**1**),[1] D (**2**), E (**3**) and apparicine.[2] The structural complexity of these alkaloids imposes a formidable challenge to synthetic organic chemists. In fact, only the total synthesis of racemic subincanadine F[3,4] and apparicine[5] has recently been reported.



Subincanadine F (**1**)



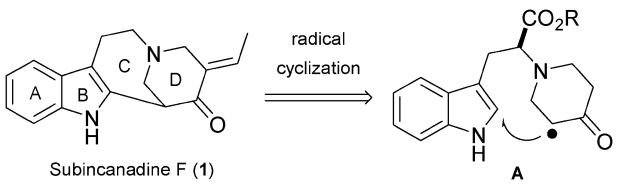
Subincanadine D (**2**, R = OH)
Subincanadine E (**3**, R = H)

(+)-Subincanadine F was isolated (in 0.002% yield) as a trifluoroacetic acid salt from a Brazilian medicinal plant, *Aspidosperma subincanum*, by Kobayashi and coworkers in 2002 with the $[\alpha]_D^{23}$ value of +17.8 (*c* 1.0, MeOH).[1] This cytotoxic compound possesses a unique 1-azabicyclo[4,3,1]decane skeleton and its absolute configuration has yet to be determined. The synthesis of racemic subincanadine F was first reported by Zhai and coworkers[3] and later by our group.[4] Herein we report the first asymmetric synthesis of (+)-subincanadine F and the assignment of its absolute configuration.

The bridged tetracyclic framework of subincanadine F requires the efficient generation of the seven-membered C ring. Previous approaches utilized the Pictet–Spengler condensation followed by skeleton rearrangement.[3,4] The intramolecular Heck coupling between *N*-protected 2-iodoindoles and a cyclohexene was also reported.[6] However, these methods were unlikely to be applicable for the asymmetric synthesis of (+)-**1**. It is therefore highly desirable to develop new methods for the stereoselective construction of the core structure. We envisioned that the uncommon 7-*endo*-trig intramolecular radical addition to an indole[7,8] depicted in Scheme 1 might provide a direct entry. The stereoselectivity of cyclization might be controlled by the ester group in intermediate **A**, thus allowing the use of easily available tryptophan as the starting material. Furthermore, unprotected indoles might be directly used in the cyclization by taking advantage of the wide functional group compatibility of radical reactions. Owing to our interest in the cyclization of α-carbonyl radicals,[9] we set out to explore this possibility.

1-(2-(1*H*-Indol-3-yl)ethyl)piperidin-4-one (**4**)[10] was first employed in our model study (Scheme 2). The reaction of **4** with trimethylchlorosilane (TMSCl) and triethylamine gave the corresponding vinyl silyl ether, which was then treated with cerium ammonium nitrate (CAN) and sodium bicarbonate to generate the α-carbonyl radical.[11] However, no desired radical cyclization product could be detected while all the starting material, **4**, decomposed. Presumably the unprotected indole and tertiary amine moieties were sensitive under the oxidative conditions.[12] To test this hypothesis, amide **5**, which was readily prepared from the condensation of 2-(1*H*-indol-3-yl)-acetic acid with piperidin-4-one followed by N-esterification with $ClCO_2Et/Et_3N$, was subjected to the above reaction conditions. Indeed, the non-optimized CAN-oxidation of the corresponding silyl ether intermediate **B** afforded the mixture of cyclized products **6** (25%) and **7** (20%), whose structures were unambiguously determined by their X-ray diffraction experiments. The formation of **7** was apparently caused by over-oxidation. These model experiments indicated that the desired radical cyclization shown in Scheme 1 was conformationally accessible. However, the cyclization should be performed under milder oxidative conditions in order to avoid over-oxidation and to allow the direct use of tertiary amine and unprotected indole as in intermediate **A**.

In light of the above model reactions, we then designed the following synthetic route towards (+)-subincanadine F starting from L-tryptophan (−)-**8** (Scheme 3). The reaction of L-tryptophan with methyl acrylate in aqueous methanol gave the double N-Michael addition product (−)-**9**. The Dieckmann condensation of (−)-**9** with the aid of excess *t*-BuOK afforded the acid (−)-**10**, which was then converted to its methyl ester (−)-**11** by treatment with methanol, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide methiodide

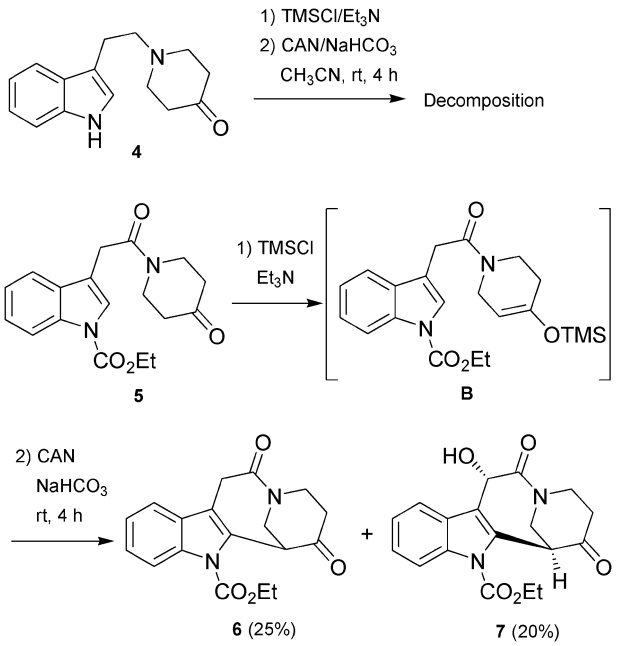


Subincanadine F (**1**)

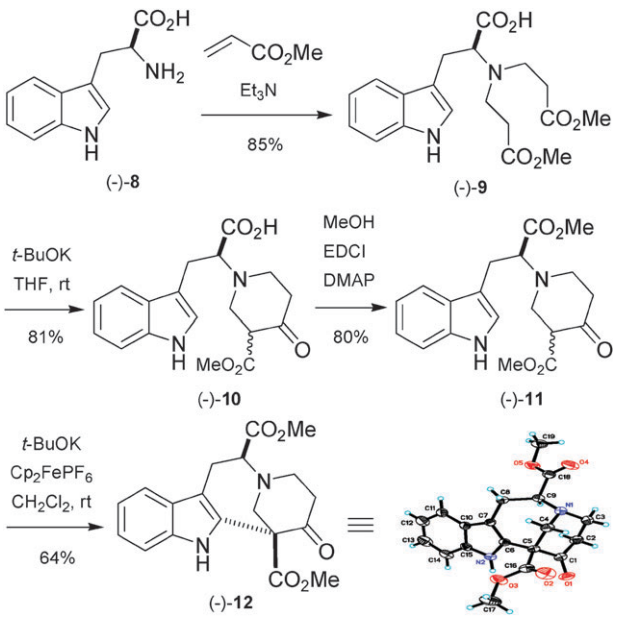
Scheme 1 Retrosynthetic analysis.

Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China. E-mail: clig@mail.sioc.ac.cn; Fax: +86-21-5492-5099; Tel: +86-21-5492-5160

† Electronic supplementary information (ESI) available: Full experimental details, characterization data and copies of ^1H and ^{13}C NMR spectra of all compounds. CCDC 790864–790866. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc03428b

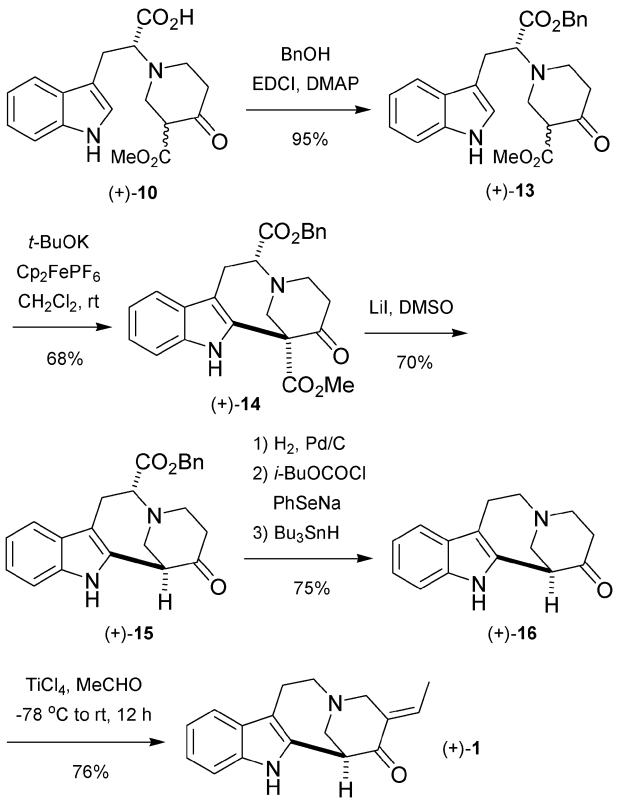


Scheme 2 Model study.



Scheme 3 Oxidative radical cyclization.

(EDCI)[13] and 4-(dimethylamino)pyridine (DMAP). The β-keto ester (−)-**11** served as the substrate for radical cyclization and various oxidative conditions were screened. Oxidants such as CAN,[10] $Mn(OAc)_3$,[11a,14] $Cu(OAc)_2$[11a,15] and $FeCl_3$,[11a,15] with or without the help of a base (K_2CO_3, MeONa or *t*-BuOK), failed to give any desired cyclization product. However, we were delighted to find that, with Cp_2FePF_6 (2.2 equiv.) as the oxidant[16] and *t*-BuOK (2.2 equiv.) as the base, the expected cyclization product (−)-**12** was isolated in 64% yield as a single stereoisomer, whose stereochemistry was firmly established by its X-ray diffraction analysis. No products derived from 6-*exo*-trig cyclization could be detected.[17]



Scheme 4 Synthesis of (+)-subincanadine F.

The cleavage of the two ester groups from (−)-**12** followed by ethylenation would lead to the target molecule. However, this turned out to be unexpectedly difficult. The six-membered D ring of **12** broke up upon treatment with aqueous LiOH or HCl (6 N) solution even at room temperature. The use of $AlCl_3$ in CH_2Cl_2 also resulted in substrate decomposition. Presumably the ring constraint made the ketone easily attacked by nucleophiles leading to retro-Dieckmann-condensation products. Nevertheless, when **12** was heated up with LiI[18] in DMSO, the four-ring skeleton remained intact. Unfortunately, the demethylation product, being an amino acid, was difficult to purify.

The above-mentioned difficulty urged us to change the protection of acid **10**. Also note that, contrary to the natural (+)-**1**, compound **12** has a negative optical rotation. Thus, D-tryptophan was used as the starting material (Scheme 4). Acid (+)-**10** was synthesized accordingly in two steps, which was then converted to the corresponding benzyl ester (+)-**13** by reaction with BnOH/EDCI/DMAP. The oxidative radical cyclization reaction of (+)-**13** was again performed under the same conditions outlined in the synthesis of (−)-**12**. The product (+)-**14** was nicely obtained in 68% yield. Treatment of compound **14** with LiI in DMSO at 180 °C now resulted in a clean reaction and (+)-**15** was achieved in 70% yield. No epimerization of the bridgehead carbon could be observed, which should be attributed to the rigid structure of (+)-**15**. The next step was the removal of benzyloxycarbonyl group. Thus, the debenzylation of **15** *via* Pd/C-catalyzed hydrogenation gave the corresponding carboxylic acid quantitatively, which, without further purification, was converted to the corresponding

phenylseleno ester in about 75% yield by reaction with *i*-BuOCOCl/PhSeNa.[19] Further treatment of the ester with Bu_3SnH/AIBN afforded cleanly the desired product (+)-**16** in almost quantitative yield.[19] Finally, the $TiCl_4$/ethyldiisopropylamine-mediated condensation of (+)-**16** with acetaldehyde furnished the target molecule (+)-**1** in a one-step procedure,[4] whose spectra were identical with those reported in the literature.[1,3,4] The chiral HPLC analysis indicated that the product was optically pure (see the ESI†). The $[\alpha]_D^{23}$ value was measured to be +198.4 (*c* 0.25, $CHCl_3$) for compound **1** and +39.2 (*c* 0.50, MeOH) for its trifluoroacetic acid salt. On the basis of the above synthesis (Schemes 3 and 4), the absolute configuration at the α-carbonyl carbon of (+)-**1** was assigned as *R*.

In conclusion, the first asymmetric total synthesis of (+)-subincanadine F was successfully accomplished and its absolute configuration was determined. Our synthesis features the unprecedented stereoselective intramolecular radical addition reaction to indoles in the uncommon 7-*endo*-trig mode, providing a convenient entry to bridged, medium-sized N-heterocycles Furthermore, the use of ferrocenium ions as a mild oxidant allows the direct use of unprotected indoles. The extension of this novel radical strategy in the synthesis of related indole alkaloids is currently in progress in our laboratory.

We thank the National Natural Science Foundation of China (Grant Nos. 20832006 and 21072211) and the National Basic Research Program of China (Grant No. 2010CB833206) for financial support.

Notes and references

1 J. Kokayashi, M. Sekiguchi, S. Shimamoto, H. Shigemori, H. Ishiyama and A. Ohsaki, *J. Org. Chem.*, 2002, **67**, 6449.
2 B. Gilbert, A. P. Duarte, Y. Nakagawa, J. A. Joule, S. E. Flores, J. A. Brissolese, J. Campello, E. P. Carrazzoni, R. J. Owellen, E. C. Blossey, K. S. Brown, Jr. and C. Djerassi, *Tetrahedron*, 1965, **21**, 1141.
3 P. Gao, Y. Liu, L. Zhang, P.-F. Xu, S. Wang, Y. Lu, M. He and H. Zhai, *J. Org. Chem.*, 2006, **71**, 9495.
4 P. Chen, L. Cao and C. Li, *J. Org. Chem.*, 2009, **74**, 7533.
5 (*a*) M.-L. Bennasar, E. Zulaica, D. Sole and S. Alonso, *Chem. Commun.*, 2009, 3372; (*b*) M.-L. Bennasar, E. Zulaica, D. Sole, T. Roca, D. Garcia-Diaz and S. Alonso, *J. Org. Chem.*, 2009, **74**, 8359.
6 D. Sole, M.-L. Bennasar and I. Jimenez, *Synlett*, 2010, 944.
7 Only $Mn(OAc)_3$- or Ru(II)-mediated 5-*exo*-trig and 6-*exo*-trig radical cyclizations to *N*-substituted indoles were reported, see: (*a*) J. Magolan and M. A. Kerr, *Org. Lett.*, 2006, **8**, 4561; (*b*) J. Magolan, C. A. Carson and M. A. Kerr, *Org. Lett.*, 2008, **10**, 1437; (*c*) J. W. Tucker, J. M. R. Narayanam, S. W. Krabbe and C. R. J. Stephenson, *Org. Lett.*, 2010, **12**, 368.
8 For an example of intermolecular radical addition to indoles, see: K. B. Lindsay, F. Ferrando, K. L. Christensen, J. Overgaard, T. Roca, M.-L. Bennasar and T. Skrydstrup, *J. Org. Chem.*, 2007, **72**, 4181.
9 (*a*) X. Fang, K. Liu and C. Li, *J. Am. Chem. Soc.*, 2010, **134**, 2274; (*b*) L. Cao and C. Li, *Tetrahedron Lett.*, 2008, **49**, 7380; (*c*) L. Liu, Q. Chen, Y.-D. Wu and C. Li, *J. Org. Chem.*, 2005, **70**, 1539; (*d*) X. Fang, H. Xia, H. Yu, X. Dong, M. Chen, Q. Wang, F. Tao and C. Li, *J. Org. Chem.*, 2002, **67**, 8481; (*e*) J. Wang and C. Li, *J. Org. Chem.*, 2002, **67**, 1271.
10 M. E. Kuehne and R. S. Muth, *J. Org. Chem.*, 1991, **56**, 2701.
11 For reviews, see: (*a*) T. Linker, in *Radicals in Organic Synthesis*, ed. P. Renaud and M. P. Sibi, Wiley-VCH, Weinheim, Germany, 2001, vol. 1, p. 219; (*b*) V. Nair, J. Mathew and J. Prabhakaran, *Chem. Soc. Rev.*, 1997, **26**, 127; (*c*) T. Sommermann, *Synlett*, 1999, 834.
12 The oxidation of tryptophan by Ce(IV) was known. See: H. D. Connor, B. E. Sturgeon, C. Mottley, H. J. Sipe, Jr. and R. P. Mason, *J. Am. Chem. Soc.*, 2008, **130**, 6381.
13 J. C. Sheehan, P. A. Cruickshank and G. L. Boshart, *J. Org. Chem.*, 1961, **26**, 2525.
14 For a review on $Mn(OAc)_3$-mediated radical reactions, see: B. B. Snider, *Chem. Rev.*, 1996, **96**, 339.
15 For comprehensive reviews on oxidative radical reactions, see: (*a*) J. Iqbal, B. Bhatia and N. K. Nayyar, *Chem. Rev.*, 1994, **94**, 519; (*b*) P. I. Dalko, *Tetrahedron*, 1995, **51**, 7579.
16 (*a*) U. Jahn, M. Muller and S. Aussieker, *J. Am. Chem. Soc.*, 2000, **122**, 5212; (*b*) U. Jahn, P. Hartmann, I. Dix and P. G. Jones, *Eur. J. Org. Chem.*, 2002, 718.
17 The preference of 7-*endo*-trig cyclization over 6-*exo*-trig cyclization should be mainly attributed to the radical-stabilizing effect of the phenyl group. For similar discussions, see: (*a*) F. Liu, K. Liu, X. Yuan and C. Li, *J. Org. Chem.*, 2007, **72**, 10231; (*b*) P. Chen, J. Wang, K. Liu and C. Li, *J. Org. Chem.*, 2008, **73**, 339.
18 (*a*) A. G. Martinez, J. O. Barcinaa, G. H. del Veccio, M. Hanack and L. R. Subramanian, *Tetrahedron Lett.*, 1991, **32**, 5931; (*b*) J. W. Fisher and K. L. Trinkle, *Tetrahedron Lett.*, 1994, **35**, 2505.
19 A. Deiters, K. Chen, C. T. Eary and S. F. Martin, *J. Am. Chem. Soc.*, 2003, **125**, 4541.

