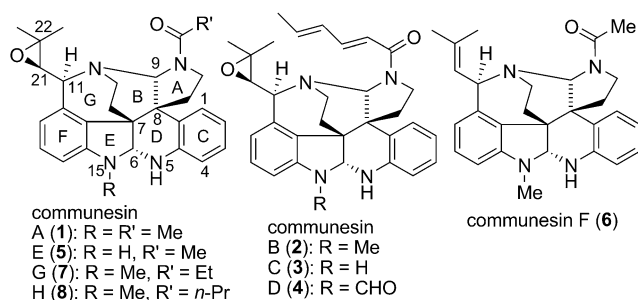


## Enantioselective Total Syntheses of Communesins A and B\*\*

Zhiwei Zuo and Dawei Ma\*

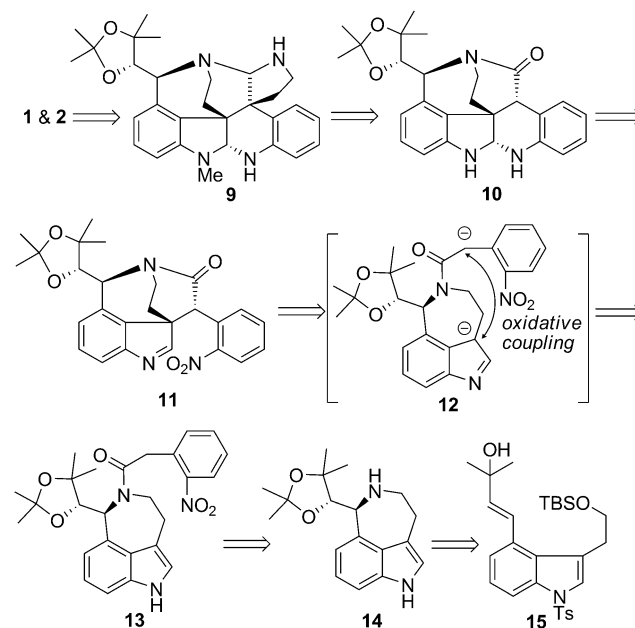
The polycyclic, tryptamine-derived indole alkaloids communesins A and B (**1** and **2**, respectively) were first isolated by Numata and co-workers in 1993 from a marine fungus of the *Penicillium* genus.<sup>[1]</sup> Their spectroscopically established structures include two contiguous quaternary centers and two fused bicyclic amins. Communesins A and B both demonstrated potent inhibition of murine lymphocytic leukemia tumor cell (P-388) proliferation in preliminary studies, with ED<sub>50</sub> values (50% effective doses) of 3.5 and 0.45  $\mu\text{g mL}^{-1}$ , respectively. In the following years, six other members of this family, namely communesins C–H (**3–8**) have been isolated from different marine sources,<sup>[2]</sup> with most having shown significant antileukemic and insecticidal activities. The remarkable biological properties and fascinating structures of these molecules have stimulated considerable interest in the synthetic community.<sup>[3–8]</sup> In the past few years, numerous elegant methods for assembling their core structures<sup>[4]</sup> and three total syntheses of communesin F have been disclosed.<sup>[5–7]</sup>



However, to date, none of the epoxide-containing family members have been synthesized, likely owing to the sensitivity of communesin F to oxidative conditions. Indeed, we have previously attempted to convert communesin F and its synthetic intermediates directly into communesin A, but all attempts were unsuccessful. We speculated that the problem is a result of the sensitivity of the amination nitrogen atoms to oxidants and therefore decided to mask the epoxide as an

oxidation-state-equivalent ketal early on in the synthesis. Obviously, this modification would force us to significantly alter our synthetic strategy. Herein, we disclose our results.

We envisioned assembling the target molecules through acylation of amine **9** and a subsequent late-stage, base-mediated epoxide synthesis (Scheme 1). Amine **9** could then



**Scheme 1.** Retrosynthetic analysis of communesins A and B. TBS = *tert*-butyldimethylsilyl, Ts = toluene-*p*-sulfonyl.

be obtained from lactam **10** through alkylation of the amide and subsequent reductive amination. We anticipated forming the hexacyclic intermediate **10** by reductive cyclization of imine **11**, which could be generated through oxidative coupling of dianion **12** generated from amide **13**.<sup>[9]</sup> Although a related oxidative coupling reaction had been successfully applied to form a spiro-fused indoline during our total synthesis of communesin F,<sup>[7]</sup> this disconnection remained daunting. Whereas the coupling in our communesin F synthesis employed a linear amide to form a single six-membered ring, the coupling in this case would require the formation of a new [3.2.2] bicyclic system with the amide nitrogen at the bridgehead, thereby breaking the nitrogen-to-carbonyl conjugation. Furthermore, in our communesin F synthesis, we had depended upon a chiral auxiliary to control the diastereoselectivity of the cyclization; it was not clear if the azepine substituent would be able to control the stereochemistry in this case. This attempt would truly test the flexibility of our oxidative coupling strategy for assembling spiro-fused indolines. The requisite amide **13** could be derived from

[\*] Z. Zuo, Prof. D. Ma

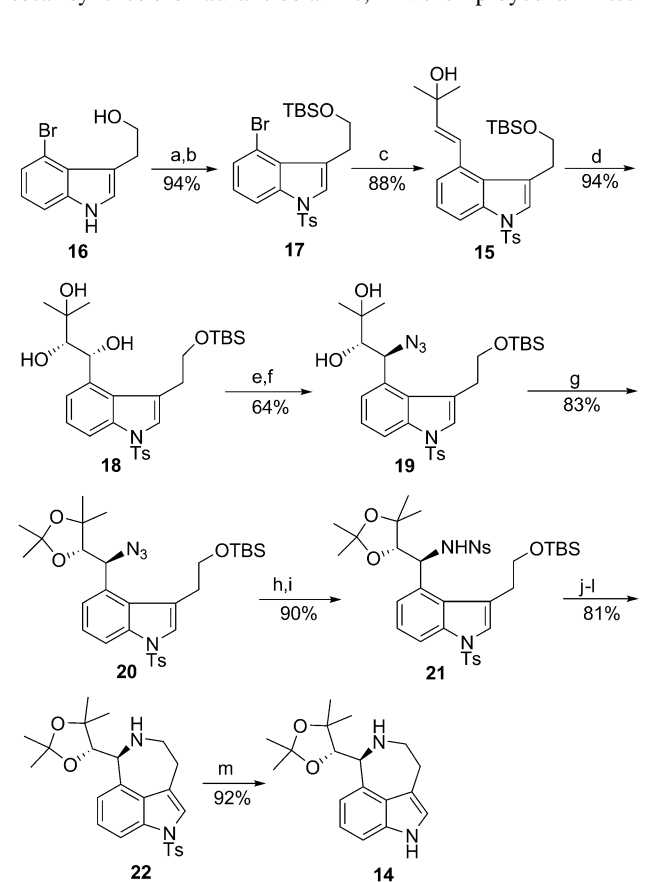
State Key Laboratory of Bioorganic & Natural Products Chemistry  
Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences  
345 Lingling Lu, Shanghai 200032 (China)  
E-mail: madw@mail.sioc.ac.cn

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aurantioclavine analogue **14**, which in turn could be prepared from olefin **15** with a Sharpless asymmetric dihydroxylation as a key step.

Our synthesis started with the preparation of auranio-clavine analogue **14** (Scheme 2). Guided by studies on the total synthesis of auranio-clavine,<sup>[10]</sup> we employed a Mitsunobu reaction<sup>[11]</sup> to form the azepine moiety of **14**.<sup>[10a]</sup>

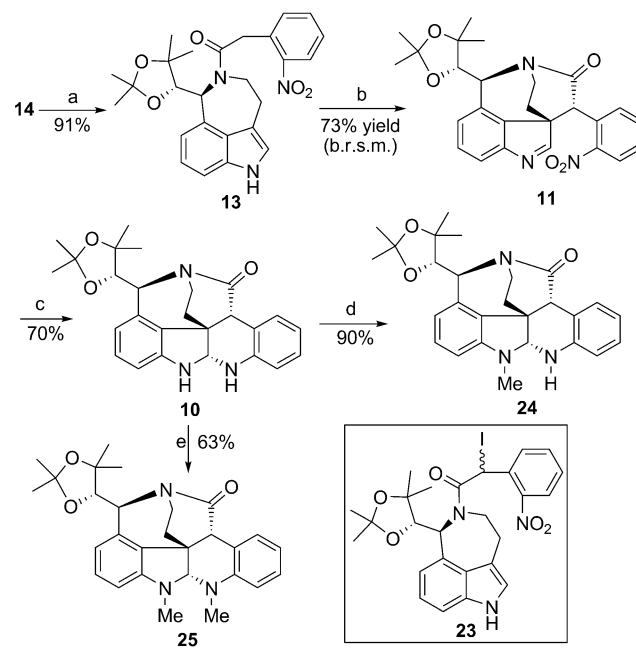


**Scheme 2.** Reagents and conditions: a) TBSCl, Et<sub>3</sub>N; b) TsCl, aq NaOH, *n*Bu<sub>4</sub>NBr, CH<sub>2</sub>Cl<sub>2</sub>; c) 3-methyl-3-hydroxybut-1-ene, Pd(OAc)<sub>2</sub>, P(*o*-Tol)<sub>3</sub>, *n*Bu<sub>4</sub>NBr, K<sub>2</sub>CO<sub>3</sub>, DMF; d) AD-mix-β, CH<sub>3</sub>SO<sub>2</sub>NH<sub>2</sub>, *t*BuOH, H<sub>2</sub>O, 96% *ee*; e) SOCl<sub>2</sub>, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; f) NaN<sub>3</sub>, *n*Bu<sub>4</sub>NBr, DMF, 90 °C; g) *p*-TsOH, DMP; h) LAH, THF; i) *o*-NsCl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>; j) TBAF, MeOH; k) P(*n*Bu)<sub>3</sub>, DEAD, THF; l) thioglycolic acid, LiOH·H<sub>2</sub>O, DMF; m) Mg, MeOH, sonication. AD-mix-β = K<sub>2</sub>OsO<sub>2</sub>(OH)<sub>4</sub>, K<sub>3</sub>Fe(CN)<sub>6</sub>, hydroquinidine 1,4-phthalazinediyl diether; DEAD = diethyl azodicarboxylate; DMAP = 4-dimethylaminopyridine; DMP = 2,2-dimethoxypropane; LAH = lithium aluminum hydride; *o*-NsCl = 2-nitrobenzenesulfonic chloride; TBAF = tetrabutylammonium fluoride.

Accordingly, silylation of alcohol **16** and subsequent tosylation provided **17**, which was subjected to a Heck reaction to afford allyl alcohol **15**. Sharpless asymmetric dihydroxylation<sup>[12]</sup> of **15** with AD-mix-β worked well, delivering the desired triol **18** in 94% yield and 96% *ee*. After treatment of **18** with thionyl chloride to form a cyclic sulfite, regioselective nucleophilic replacement with sodium azide was carried out to obtain azide **19**. Protection of the diol in **19** with DMP led to the formation of ketal **20**, which was further reduced with LAH, and treated with 2-nitrobenzenesulfonic chloride to

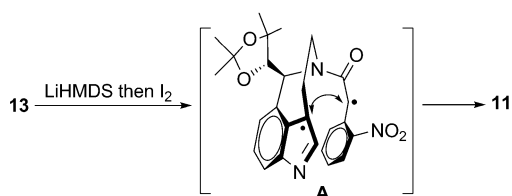
give sulfonamide **21**.<sup>[13]</sup> After cleavage of the silyl ether in **21** with TBAF, the liberated alcohol was exposed to DEAD and tri-*n*-butylphosphine to provide a cyclized product,<sup>[11]</sup> which was hydrolyzed to deliver azepine **22**. Desulfonation of **22** using magnesium and methanol furnished **14** with 92% yield.

Condensation of azepine **14** with 2-(2-nitrophenyl)acetic acid under the assistance of BOPCl gave rise to amide **13** (Scheme 3). With this intermediate in hand, we investigated the key oxidative coupling reaction. Initially, we attempted



**Scheme 3.** Reagents and conditions: a) 2-(2-nitrophenyl)acetic acid, BOPCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>; b) LiHMDS, then iodine, THF, −78 °C; c) Raney-Ni, H<sub>2</sub>, MeOH; d) KHMDS then MeI; e) 37% HCHO, NaBH(OAc)<sub>3</sub>. BOPCl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride, LiHMDS = lithium hexamethyldisilazane, b.r.s.m. = based on recovered starting material.

this reaction under our previous conditions (LiHMDS, THF, −78 °C, then I<sub>2</sub>, −78 °C to RT), and found that only the iodination product **23** was produced as a diastereomeric mixture. However, when iodine was added at room temperature, we isolated the desired spiro-fused, twisted-amide-containing indoline **11** (73% yield based on 11% recovery of **13**) as a single isomer. No further cyclization of **23** occurred, thus indicating that the formation of **11** did not involve an S<sub>N</sub>2 reaction. Next, reduction of the nitro group in **11** by Raney-Ni-catalyzed hydrogenation and the subsequent spontaneous attack of the resultant amine at the imine moiety afforded hexacyclic intermediate **10**. Selective methylation at N15 to provide the desired intermediate **24** was achieved by treatment of **10** with KHMDS and iodomethane. Notably, when **10** was subjected to reductive amination with formaldehyde, dimethylated product **25** was isolated. X-ray structural analysis of **25** confirmed that the newly created stereocenters possessed the requisite configuration for synthesizing the target molecules.<sup>[14]</sup>

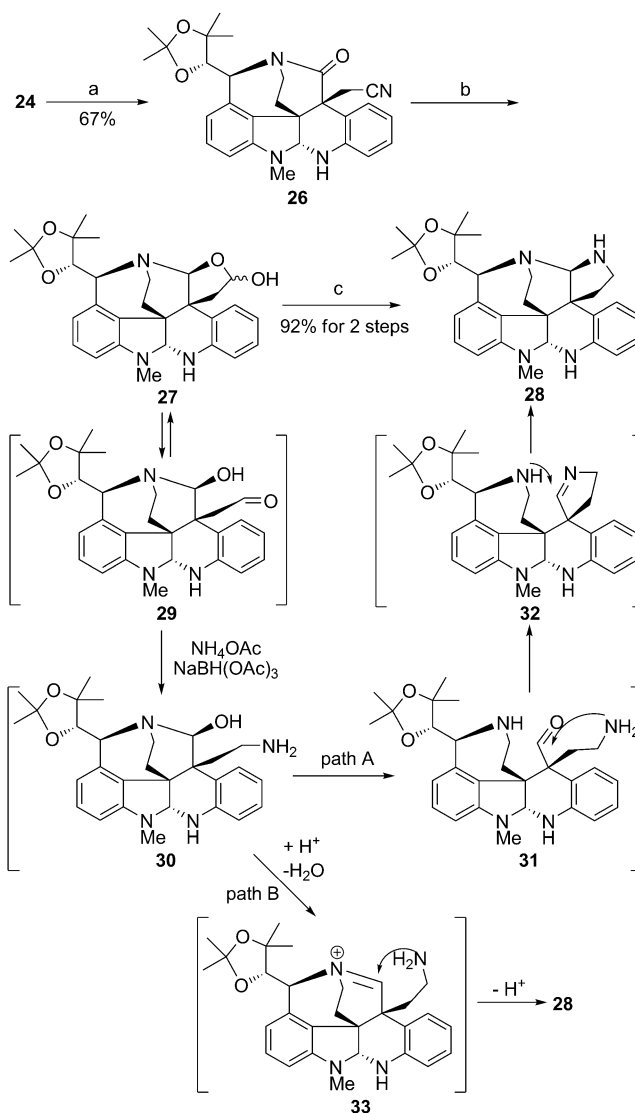


**Scheme 4.** Possible stereochemical course for conversion of amide **13** into spiro-fused indoline **11**.

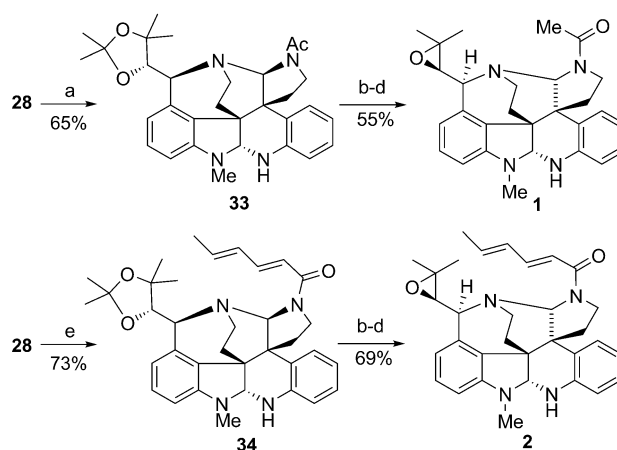
The stereochemical outcome during the formation of **11** could be rationalized by a proposed transition-state model (Scheme 4). After treatment of **13** with LiHMDS and subsequent oxidation with iodine, the diradical transition state **A** might form, in which the rigid conformation was strengthened by the favorable stacking interaction between the electron-deficient arene and indole moieties, and the diradical combined from the opposite site of the bulky 1,3-dioxolane group to give **11** as a single isomer.

After we established the hexacyclic system of communesins A and B, the stage was set for introducing the A ring. In previous protocols for synthesizing communesin F, allylation of a pentacyclic intermediate at the C8 position was employed for obtaining the required two carbon side chain.<sup>[6,7]</sup> However, in case of **24**, allylation (with KOrBu/allyl iodide) was found to give an O-allylation product exclusively, which could not be converted into the desired product through a Claisen rearrangement as described by the Qin group.<sup>[5]</sup> To solve this problem, a number of alkylation reagents and reaction conditions were screened. We were pleased to find that a combination of KHMDS and 2-iodoacetonitrile afforded C-alkylation product **26** with 67% yield. We discovered that the following reaction sequence could be utilized for highly efficient A-ring formation: LAH reduction of **26** delivered lactol **27**, and subsequent treatment of **27** with ammonium acetate and NaBH(OAc)<sub>3</sub> produced amina **28** (in 92% yield from **26**). The transformation of **27** to **28** might have proceeded through two possible cascade reaction processes (Scheme 5). The lactol ring of **27** might have first been opened to yield aldehyde **29**, which would have undergone reductive amination to primary amine **30**. Next, the semilactam ring of **30** may have opened to form intermediate **31** (path A; examples of similar ring openings in reduction of bridged lactams have been reported<sup>[15]</sup>), and the intramolecular condensation of **31** would have afforded imine **32**. Finally, intramolecular attack of the secondary amine onto the imine moiety would have delivered amina **28**. Alternatively, direct dehydration of **30** might have afforded bridgehead iminium ion **33**, which would further react with the amine moiety to furnish **28** (path B).

The completion of the syntheses of communesins A and B is outlined in Scheme 6. Acylation of **28** produced amide **33**, which was deprotected under acidic conditions, reacted with mesyl chloride, and then treated with potassium carbonate in methanol to afford communesin A. In a parallel procedure, condensation of **28** with sorbic acid under the activation of BOPCl led to the formation of amide **34**, which was subjected to a similar deprotection–mesylation–epoxidation ring-for-



**Scheme 5.** Reagents and conditions: a) KHMDS then ICH<sub>2</sub>CN, THF, –78°C to RT; b) LAH, THF; c) NH<sub>4</sub>OAc, NaBH(OAc)<sub>3</sub>, MeOH.



**Scheme 6.** Reagents and conditions: a) Ac<sub>2</sub>O, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>; b) CF<sub>3</sub>CO<sub>2</sub>H, H<sub>2</sub>O; c) MsCl, pyridine, CH<sub>2</sub>Cl<sub>2</sub>; d) K<sub>2</sub>CO<sub>3</sub>, MeOH; e) sorbic acid, BOPCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>. Ms = methanesulfonyl.

mation process as described above to furnish communesin B. The analytical data of synthetic **1** and **2** are in agreement with those reported for the natural (–)-communesins A and B, respectively.

In conclusion, we have achieved the first total syntheses of communesins A and B with the longest linear sequence for each of 24 steps from 4-bromotryptophol and overall yields of approximately 2% and 3%, respectively. The successful construction of key intermediate **11** by oxidative coupling further demonstrates the flexibility of our strategy for assembling spiro-fused indolines. Moreover, our efficient installation of the A ring in communesins A and B by reductive lactol amination sets a new precedent in the synthesis of amination-embodied natural products. Finally, our synthetic route opens a new avenue for generating analogues of communesins with a higher formal oxidation state and will facilitate the establishment of structure–activity relationships for these marine alkaloids.

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