Synthetic Studies towards Communesins: Diastereoselective Oxidative Rearrangement of Aurantioclavine Derivatives

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Abstract: Communesins are a heptacyclic class of indole alkaloids bearing two aminal moieties and two contiguous quaternary carbon centers. We have investigated the construction of the pentacyclic skeleton of communesins via the oxidative rearrangement of aurantioclavine derivatives, because aurantioclavine is believed to be a biosynthetic intermediate of the polycyclic communesin alkaloids. The C7 quaternary carbon center was constructed in a stereoselective manner, while the installation of the C11 stereocenter required an epimerization process. The isolation of 2-ethoxyindolenine prior to the reduction of the nitro group and cyclization was found to be critical to the success of this strategy.

Introduction

Communesins are a heptacyclic class of indole alkaloids bearing two aminal moieties and two contiguous quaternary carbon centers that can isolated from a marine fungal strain of *Penicillium* species (Figure 1).[1,2] These alkaloids have been reported to show significant cytotoxicity against P388 lymphocytic leukemia cells (A, B: ED_{50} = 3.5 and 0.45 μg/mL respectively), as well as potent insecticidal activity towards silkworms (B, E: LD_{50} = 5 and 80 μg/g). These molecules have also attracted considerable interest as synthetic targets because of their complex structures and significant biological activities.[3] Several total syntheses have been reported to date for the construction of racemic communesins, including those of Qin[4], Weinreb[5], Ma[6a] and Funk.[7] Furthermore, Ma *et al.*[6b] also reported the development of an asymmetric total synthesis of communesins. Interestingly, Stoltz and co-workers reported that aurantioclavine, which is a tricyclic alkaloid isolated from *Penicillium aurantiovirens,*[8] could be a biosynthetic intermediate of the polycyclic communesin alkaloids.[9,10] In a separate study, Stoltz *et al,*[11] reported a formal synthesis of (±)-communesin F using a unified stereodivergent alkylation approach, as well as a biosynthesis-inspired approach from aurantioclavine. Tang *et al.*[12] confirmed that communesins can biosynthesized by the coupling of tryptamine and aurantioclavine based on a series of genetic-inactivation studies.[12]

We recently reported the development of an enantioselective total synthesis of aurantioclavine based on a Pd-catalyzed asymmetric allylic amination reaction.[13] Given that communesins share their core structure with aurantioclavine, it was envisaged that our recently developed route could be applied to the asymmetric synthesis of communesins. Furthermore, if we could achieve the synthesis of communesins from intermediate **6** for aurantioclavine, then it would possible to prepare a wide range of synthetic analogs for biological studies using the same synthetic route. With this in mind, we investigated the possibility of extended of our previous methodology to the construction of communesins.

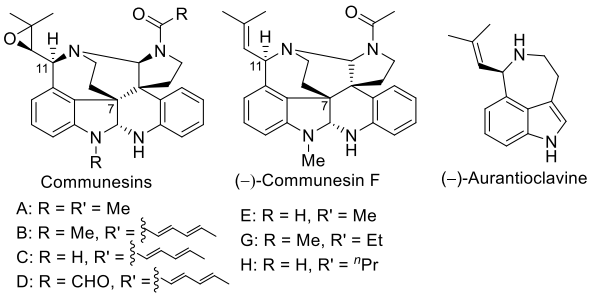

Figure 1. Communesins and (–)-Aurantioclavine.

It was envisioned that the communesins could be synthesized from pentacyclic compound **1** bearing a C7 quaternary carbon center. Compound **1** itself could be prepared from **6** via one of two different synthetic routes (Scheme 1). According to the first of these two routes, pentacyclic skeleton **1** could be constructed by the Pd-catalyzed cyclization[14] of amidine **2**, which could itself be constructed by the SmI_2-mediated reductive cyclization[15] of carbodiimide **3** (route A). It is noteworthy that SmI_2-mediated reductive cyclization reactions of this type represent a powerful and reliable strategy for the synthesis of 2-iminoindolines. The second potential strategy for the construction of compound **1** involved the oxidative rearrangement of the 2-substituted indole **5**, which contains the same skeleton as aurantioclavine, to give **4**. The subsequent cyclization of **4** would then give the desired pentacyclic compound **1** (route B). The use of an oxidative rearrangement reaction for the synthesis of 3,3-disubstituted oxindoles is a well established method in organic chemistry, and this strategy has been used before for the construction of an indole alkaloid.[16] Notably, the two important intermediates **3** and **5** could be derived from common intermediate **6**, which we prepared previously in our synthesis of (–)-aurantioclavine. In this study, we describe our efforts towards the synthesis of the pentacyclic skeleton **1** based on the two synthetic routes described above. The isolation of 2-ethoxylindolenine from the oxidative rearrangement reaction was found to be critical to the success of this strategy, because it prevented the occurrence of any undesired side reactions.

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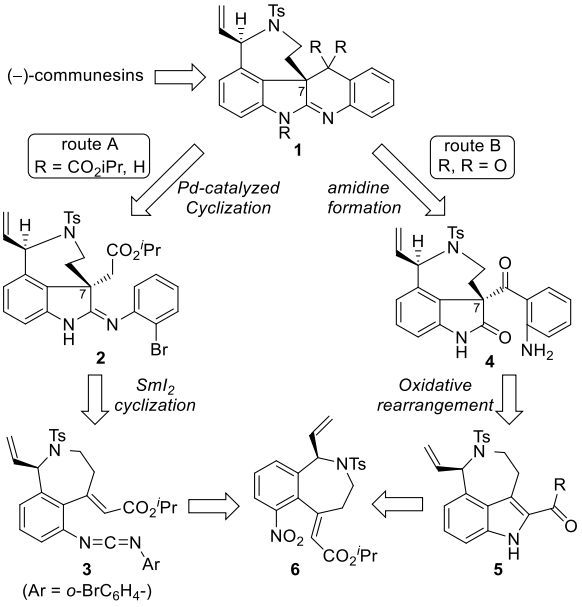
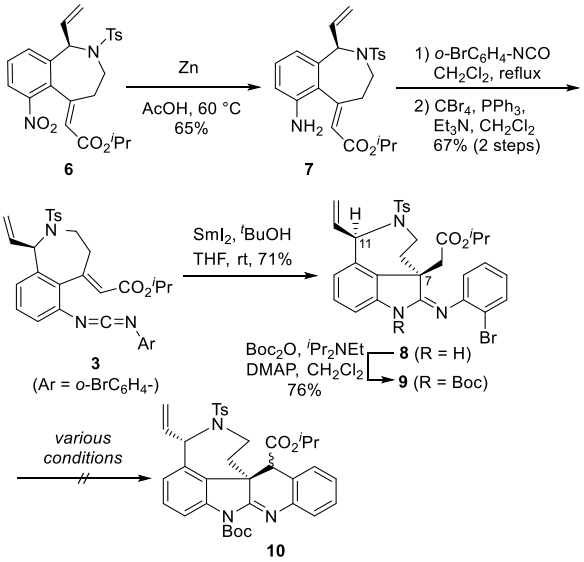


Scheme 1. Retrosynthesis of the pentacyclic core of Communesins.

Results and Discussion

We initially investigated the synthesis of carbodiimide **3**[13] to explore the feasibility of using sequential SmI_2-mediated reductive cyclization and Pd-catalyzed cyclization reactions. The reduction of the nitro group in azepane **6**[17] gave aniline **7** (Scheme 2). The subsequent treatment of **7** with *o*-BrC_6H_4NCO gave the corresponding urea, which was converted to carbodiimide **3** following a dehydration reaction with CBr_4 and PPh_3. The amidine core bearing the desired quaternary carbon center was successfully constructed using a SmI_2-mediated reductive cyclization reaction.[14] Disappointingly, however, the C7 stereochemistry was the undesired configuration. The formation of the undesired stereochemistry at C7 can be explained in terms of the differences in the stabilities of the different conformers of compound **3** (Figure 2). Conformer **A** would be thermodynamically more stable than conformer **B** because the Ts and vinyl groups would be axial, which would minimize the steric repulsion between these two groups. With this in mind, the reaction would proceed through conformer **A** to give cyclized compound **8**.[18] The subsequent Boc protection of the indoline nitrogen gave compound **9** as a single diastereomer, and both of these compounds were screened against an extensive series of Pd-catalyzed conditions in an attempt to affect their cyclization to give the desired pentacyclic compound **10**.[14] However, none of the conditions tested provided access to compound **10**. For example, the treatment of **9** with $Pd(OAc)_2$, PPh_3 and Cs_2CO_3 in toluene at 80 °C gave a complex mixture. Furthermore, the use of other ligands[19] and bases[20] also resulted in the decomposition of the starting material. Given that the α position of the ester would be congested under the conditions required of Pd-mediated catalysis, it would be difficult for the Pd-intermediate derived from the oxidative addition of the aryl bromide to Pd(0) to react with the enolate. With this in mind, we switched our focus the second of the two plans described above (i.e. route B, Scheme 1), where the fifth ring would be cyclized via the formation of an amidine.[5,8]



Scheme 2. Attempted formation of the amidine ring by a Pd-catalyzed cyclization.

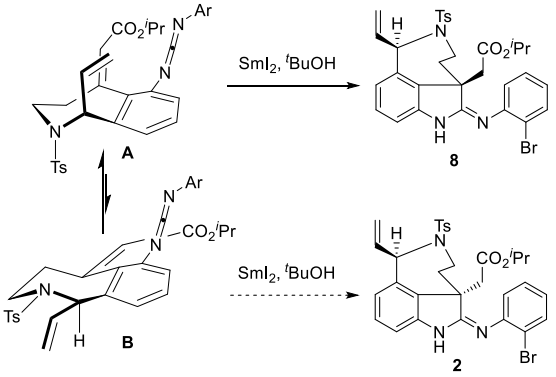
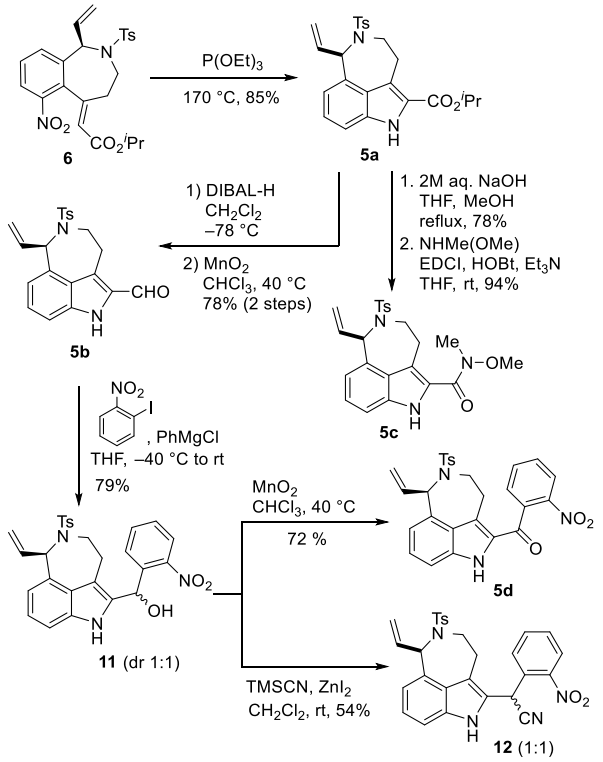


Figure 2. Stereochemistry of SmI_2-mediated reductive cyclization of **3**.

To evaluate the feasibility of the second strategy, we prepared several 2-substituted indoles for the oxidative rearrangement reaction. The treatment of compound **6** with $P(OEt)_3$ at 170 °C gave ester **5a**, which was subjected to a hydrolysis reaction followed by a condensation reaction with *N*-methoxymethylamine to give Weinreb amide **5c** (Scheme 3). The subsequent reduction of **5a** with DIBAL-H, followed by the allylic oxidation of the resulting alcohol gave aldehyde **5b**. The nucleophilic addition of an *in situ* generated Grignard reagent to the aldehyde gave the corresponding alcohol **11**, which was treated with MnO_2 to give ketone **5d**. Compound **12** was also

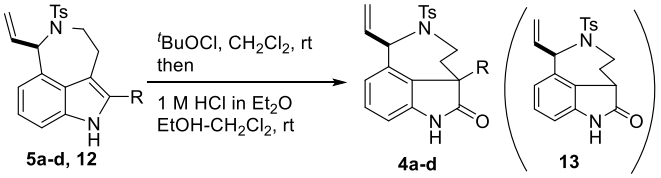
prepared from alcohol **11** to determine the importance of the carbonyl group.



Scheme 3. Synthesis of substrates **5a**–**d** and **12** for the oxidative rearrangement.

With a series of 2-substituted indoles in hand (**5a**–**d** and **12**), we proceeded to investigate the oxidative rearrangement of these compounds for the synthesis of oxindoles bearing a quaternary carbon center at C7. The chlorination of ester **5a** with ^{t}BuOCl, followed by the treatment of the resulting species with 1 M HCl in EtOH-CH_2Cl_2 gave the desired oxindole **4a** (Table 1, entry 1). Although the reaction of aldehyde **5b** under the same conditions gave oxindole **13** instead of the desired compound **4b**, Weinreb amide **5c** was converted to **4c** in 62% yield (Table 1, entries 2 and 3). These results were consistent with the results reported by Moody.[16a] Compound **13** was most likely produced by the retro-Claisen-type reaction of **4b** following its oxidative rearrangement. Ketone **5d** reacted smoothly under these conditions to give the desired compound **4d**. In contrast, the reaction of **12**, which did not contain a carbonyl group, gave a complex mixture of products (Table 1, entries 4 and 5). These results therefore indicated that the presence of a carbonyl group was important for stabilizing the transition state of the rearrangement step.

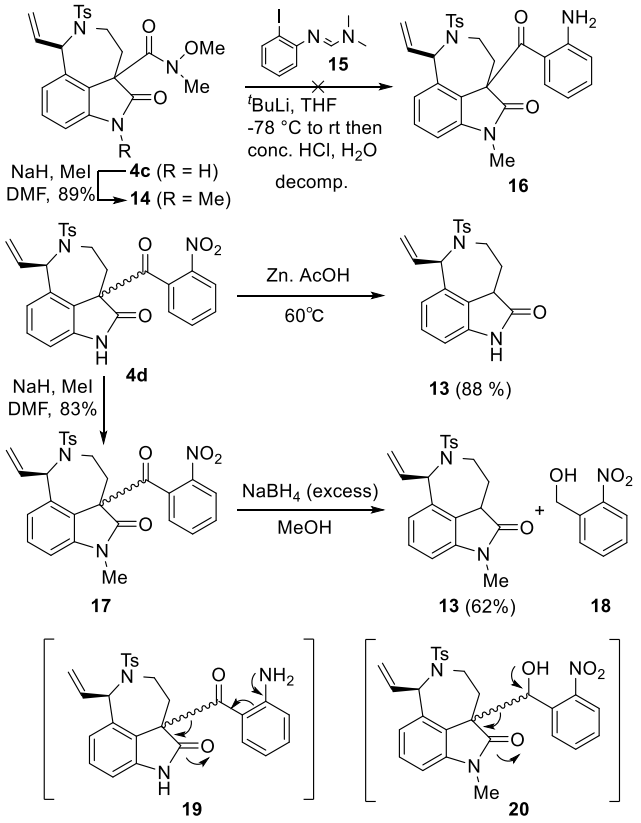
Table 1. Oxidative rearrangement of compounds **5a–d** and **12**.



Entry	Substrate	R	Results[a]
1	**5a**	-$CO_2{}^i$Pr	**4a** (54%)
2	**5b**	-CHO	**4b** (0%), **13** (80%)
3	**5c**	-CONMe(OMe)	**4c** (62%)
4	**5d**		**4d** (88%)
5	**12**		Complex mixture

[a] Isolated yield.

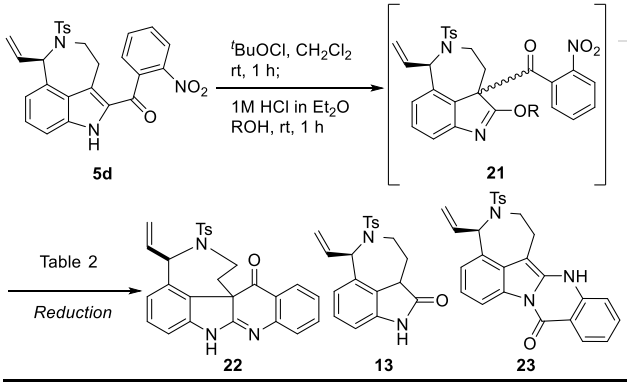
We then attempted to access a cyclized precursor from compounds **4c** and **4d** (Scheme 4). The protection of the indole nitrogen in **4c** with a methyl group gave compound **14**, which was treated with an *in situ*-generated aryl lithium reagent prepared from iodide **15** and ^{t}BuLi in an attempt to prepare compound **16**. However, this reaction resulted in the decomposition of the substrate. The reaction of **4d** with zinc in acetic acid led to the reduction of the nitro group followed by the cleavage of the C–C bond at the 3-position of the oxindole core to give compound **13**. The cleavage of the C–C bond was attributed to the delocalization of the electron pair of the newly formed aniline **19**.[21] Furthermore, the reduction of ketone **17**, which was prepared from **4d**, also gave product **13** via a similar retro-aldol-type reaction through compound **20**. Based on these results, we concluded that the oxindole moiety was the cause of the undesired retro-aldol-type reactions, and that it would therefore need to be protected prior to the reduction of nitro and carbonyl groups.



Scheme 4. Attempted derivatization of **4c** and **4d**.

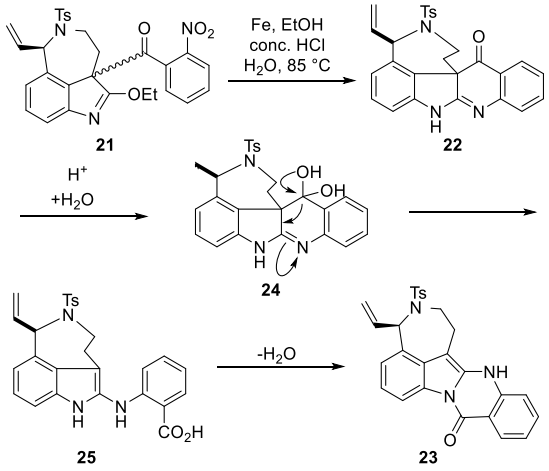
To address the issues described above, we selected 2-alkoxyindolenine, which is an intermediate of the oxidative rearrangement reaction, as a suitable protecting group for the reduction of the nitro group. Given that 2-ethoxyindolenine **21** was not isolated during the course of our initial evaluation of the oxidative rearrangement reaction, as shown in Table 1, it was anticipated that this compound would be unstable under the reaction conditions or its subsequent purification by column chromatography over silica gel. With this in mind, the reduction of **21** was performed immediately after its formation and concentration without any further purification. Although the reduction of **21** with $SnCl_2$ in toluene gave a complex mixture, the use of Zn gave compounds **13** and **23**[22] in 54 and 14% yields, respectively (Table 2, entries 1 and 2). When the reduction was conducted in the presence of Fe, the reaction gave a small amount of **23** as part of a complex mixture (Table 2, entry 3). When isopropanol was used instead of ethanol to stabilize the 2-alkoxyindolenine intermediate, 2-isopropoxyindolenine was obtained as an intermediate. However, the oxidative rearrangement of this intermediate did not proceed smoothly, and the subsequent treatment of this material with Zn gave a complex mixture (Table 2, entry 4). The reduction was also conducted without the concentration of the 2-ethoxyindolenine solution, but gave only compound **23** in 47% yield (Table 2, entry 5). We speculated that the by-product **23** would be produced by the formation of the pentacyclic skeleton **22**, followed by a retro-Claisen-type reaction and the formation of an indoloquinazolinone (Scheme 5). In fact, compound **22** was observed in the ^{1}H NMR spectrum of a crude reaction mixture when a shorter reaction time was used. Furthermore, it was possible to isolate this material together with 2-ethoxyindolenine **21** by silica gel column chromatography in low yields of 21 and 28%, respectively (Table 2, entry 6). After the isolation of **21**, it was also confirmed that **21** could be readily converted to indoloquinazolinone **23** under acidic conditions (Scheme 5).

Table 2. Investigation of the construction of the pentacyclic skeleton.



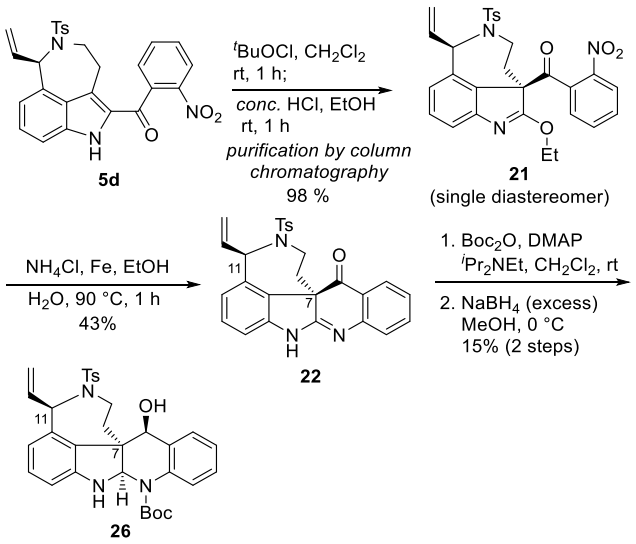
Entry	R	Conditions	Results[b]
1	Et	$SnCl_2$, toluene, 70 °C, 2 h	Complex mixture
2	Et	Zn, AcOH, toluene, 85 °C, 2 h	**13** (54%), **23** (14%)
3	Et	Fe, AcOH, toluene, 85 °C, 2 h	**23** (<15%)
4	iPr	Zn, AcOH, toluene, 85 °C, 2 h	Complex mixture
5 [a]	Et	Zn, H_2O, 90 °C, 3 h	**23** (47%)
6 [a]	Et	Fe, H_2O, 90 °C, 45 min	**13** (16%), **23** (11%), **21** (28%), **22** (21%)

[a] Conc. HCl was used for the first step and the solvent was not evaporated before the reduction. [b] Isolated yield.



Scheme 5. Conversion of 2-ethoxyindolenine **21** to indoloquinazolinone **23**.

Finally, we successfully isolated 2-ethoxyindolenine **21** in 98% yield by the treatment of **5d** with ^{t}BuOCl followed by conc. HCl in EtOH. The subsequent reaction of **21** under mildly acidic conditions (i.e., Fe and solid NH_4Cl in EtOH-H_2O at 90 °C) gave the pentacyclic compound **22** in 43% yield without the formation of any of the undesired indoloquinazoline **23** (Scheme 6). The stereochemistry at C7 was determined after the Boc protection and subsequent reduction of the amidine nitrogen to give **26**. The NOESY spectra of **26** revealed that H^a was correlated with H^b and H^c, and that H^d was correlated with H^e and H^f (Figure 3). These results therefore indicated that the C7 stereochemistry was *R*, and that the epimerization of C11 would be required for the construction of the communesin core.[23]



Scheme 6. Synthesis of the pentacyclic skeleton **22**.

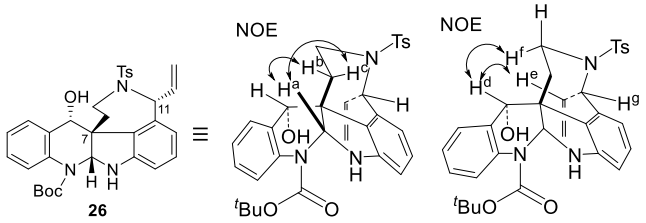
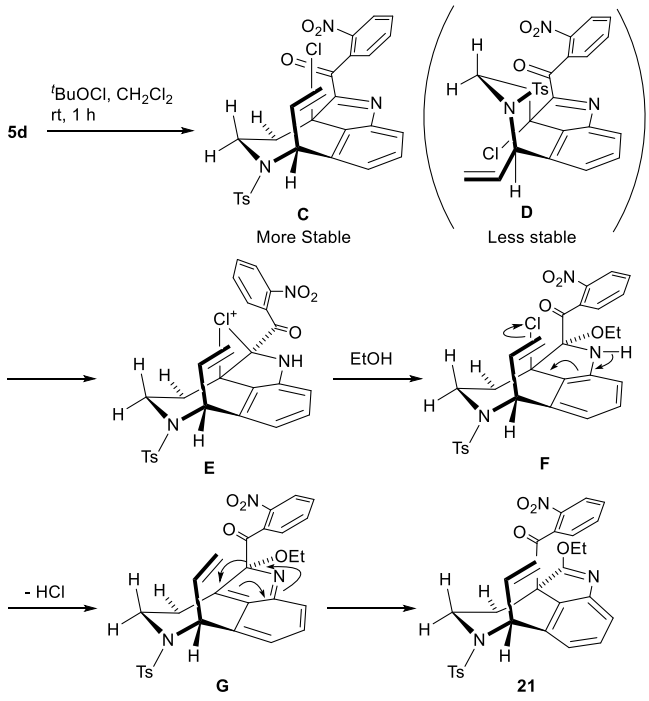


Figure 3. NOESY experiments with compound **26**.

Based on the results of several previous reports,[16b,c,f,i-l] the diastereoselectivity of the oxidative rearrangement can be rationalized as follows. The treatment of **5d** with ^{t}BuOCl would give 3-chloroindolenine **C**, which would be thermodynamically more stable than **D** (Scheme 7). The protonation of **C** and formation of chloronium cation **E** would be followed by the addition of EtOH to give intermediate **F**. In this case, the rearrangement would occur via an S_N1 reaction rather than an S_N2 reaction. The elimination of the chloride ion and the diastereoselective rearrangement of the carboaryl moiety would therefore proceed through intermediate **G** to give 2-ethoxyindolenine **21**.



Scheme 7. Stereochemistry of oxidative rearrangement of **5d**.

Conclusions

We have investigated the construction of the pentacyclic skeleton of the communesins through two synthetic strategies, including i) a SmI_2-mediated reductive cyclization and Pd-

catalyzed cyclization strategy; and ii) an oxidative rearrangement strategy. Although the first of these two strategies was found to be unsuccessful, the desired pentacyclic skeleton was successfully constructed using the second strategy. The C7 quaternary carbon center was constructed in a stereoselective manner based on an oxidative rearrangement reaction, while the C11 stereocenter required an epimerization step to afford the desired stereochemistry. Finally, the isolation of 2-ethoxyindolenine prior to the reduction of its nitro group was found to be critical to the success of the cyclization reaction. We are currently investigating the epimerization of the C11 carbon center with the aim of developing an enantioselective total synthesis of the communesins.

Experimental Section

General: All of the non-aqueous reactions were carried out under a positive atmosphere of argon in dried glassware. Analytical thin-layer chromatography was performed with Silica gel 60 (Merck). Silica gel column chromatography was performed over Kanto silica gel 60 (particle size, 63–210 μm) and Fuji silysia Chromatorex BW-300. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL JNM-ECA 500 system (JEOL, Japan) at 500 MHz or a JEOL JNM-AL 400 system at 400 MHz. Chemical shifts have been reported relative to Me_4Si (δ 0.00) in $CDCl_3$. The multiplicities of the signals in the spectra have been described by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL JNM-ECA 500 system at 126 MHz or a JEOL JNM-AL 400 system at 100 MHz. Chemical shifts have been reported relative to $CDCl_3$ (δ 77.0). Infrared spectra were recorded on a FT/IR-4100 Fourier-transform infrared spectrometer with attenuated total reflectance (JASCO, Japan). Low and High resolution mass spectra were recorded on JEOL JMS-HX/HX 110A mass spectrometer for FAB-MS and a Shimadzu LCMS-IT-TOF (Shimadzu, Japan) for ESI-MS.

Material: Anhydrous CH_2Cl_2, THF, methanol and ethanol were purchased from KANTO Chemical Co. Aldrich and Wako chemicals. The reagents and materials used in the current study were obtained from Tokyo Chemical Industry Co., Ltd, Aldrich Inc. and several other commercial suppliers and used without further purification.

Compound 5a: A solution of **6** (792 mg, 1.69 mmol) in $P(OEt)_3$ (4.0 mL) was stirred at 170 °C for 3 h. The mixture was then concentrated under reduced pressure and purified by flash column chromatography over neutral silica gel (20% EtOAc/hexane) to give **5a** (633 mg, 85%) as a colorless oil: $[\alpha]_D^{21}$ –51.7 ° (*c* 1.12, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.04 (1H, br s), 7.69 (2H, d, *J* = 8.3 Hz), 7.27-7.26 (1H, m), 7.20 (1H, t, *J* = 7.7 Hz), 7.15 (2H, d, *J* = 8.0 Hz), 6.84 (1H, d, *J* = 7.2 Hz), 6.04 (1H, s), 5.77 (1H, ddd, *J* = 17.1, 10.4, 4.5 Hz), 5.30-5.25 (1H, m), 5.13 (1H, d, *J* = 10.3 Hz), 4.68 (1H, d, *J* = 17.3 Hz), 4.05-4.03 (1H, m), 3.60-3.54 (2H, m), 3.44-3.37 (1H, m), 2.34 (3H, s), 1.39 (3H, d, *J* = 2.6 Hz), 1.38 (3H, d, *J* = 2.6 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7, 142.9, 138.0, 137.7, 136.8, 134.0, 129.3, 126.9, 125.2, 124.5, 123.2, 121.6, 120.2, 119.1, 110.6, 68.5, 63.8, 43.2, 29.8, 22.0 (x2), 21.3; IR (ATR, cm^{-1}) 3344, 2980, 1693, 1452, 1338, 1248, 1156, 1094, 916, 751; HRMS (ESI) calcd for $C_{24}H_{27}N_2O_4S$ $[M+H]^+$ 439.1686; Found: *m/z* 439.1668.

Compound 5b : To a solution of **5a** (200 mg, 0.456 mmol) in CH_2Cl_2 (5 mL) was added DIBAL-H (1 M in hexane, 1.6 ml, 1.6 mmol) at −78 °C, and the mixture was stirred at −78 °C for 1 h. The reaction mixture was then quenched with satd. aq. Na/K tartrate and stirred vigorously at room temperature for 1 h. The mixture extracted with EtOAc, washed with brine and dried over Na_2SO_4. Concentration under reduced pressure gave the crude alcohol without purification. To a solution of the crude alcohol in $CHCl_3$ (20 mL) was added MnO_2 (705 mg, 8.11 mmol) at room temperature, and the mixture was stirred at 40 °C for 1 h. After reaction mixture was filtered through a pad of Celite, and concentration under reduced pressure. The crude material was purified by flash column chromatography on silica gel (30 % EtOAc/hexane) to give **5b** (124 mg, 76%, 2 steps) as a white amorphous: $[\alpha]_D^{22}$ –42.8 ° (*c* 0.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.94 (1H, s), 8.94 (1H, br s), 7.69 (2H, d, *J* = 6.9 Hz), 7.30-7.28 (2H, m), 7.19 (2H, d, *J* = 7.4 Hz), 6.90-6.89 (1H, m), 6.06 (1H, br s), 5.79-5.75 (1H, m), 5.16 (1H, d, *J* = 10.3 Hz), 4.67 (1H, d, *J* = 17.2 Hz), 4.11-4.08 (1H, m), 3.65 (1H, td, *J* = 10.2, 5.1 Hz), 3.53-3.49 (2H, m), 2.37 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 180.3, 143.2, 138.4, 137.9, 137.4, 135.4, 131.3, 129.5, 127.0, 126.8, 126.2, 125.2, 120.8, 119.6, 111.2, 63.6, 43.0, 27.6, 21.5; IR (film, cm^{-1}) 3317, 2981, 2918, 1649, 1574, 1535, 1460, 1369, 1341, 1278, 1236, 1158, 1092, 1019, 974, 915, 876, 755, 736, 691, 667; HRMS (FAB) calcd for $C_{21}H_{21}N_2O_3S$ $[M+H]^+$ 381.1273; Found: *m/z* 381.1272.

Compound 5c: To a solutions of **5a** (150 mg, 0.379 mmol) in MeOH (4 mL) and THF (4 mL) was added a solutions of 2M aq. NaOH (4 mL). The mixture was refluxed for 1 h, and then concentration under reduced pressure until THF and MeOH were removed. The residue was acidified with 2M aq. HCl (4 mL) and extracted with EtOAc, dried over Na_2SO_4. After concentration under reduced pressure, a crude carboxylic acid was obtained as a white solid. To a solution of crude in THF (8 mL) was added NHMe(OMe) (56 mg, 0.568 mmol), EDCI (109 mg, 0.568 mmol), HOBt (77mg, 0.568 mmol) and Et_3N (0.159 mL, 1.14 mmol) at room temperature. This mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel (30% EtOAc/hexane) to give the mixture of **5c** (156 mg, 94 %) as a white amorphous: $[\alpha]_D^{22}$ –39.4 ° (*c* 0.27, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (1H, br s), 7.68 (2H, d, *J* = 8.3 Hz), 7.26-7.21 (2H, m), 7.14 (2H, d, *J* = 8.0 Hz), 6.88 (1H, d, *J* = 6.9 Hz), 6.09 (1H, s), 5.84-5.81 (1H, m), 5.14 (1H, d, *J* = 10.3 Hz), 4.71 (1H, d, *J* = 16.9 Hz), 4.01 (1H, d, *J* = 14.9 Hz), 3.68 (3H, s), 3.63-3.53 (2H, m), 3.41-3.34 (4H, m), 2.34 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.9, 142.7, 138.2, 138.0, 136.4, 133.8, 129.5, 129.3, 127.0, 124.7, 124.2, 123.7, 122.5, 120.2, 119.0, 110.5, 63.8, 61.8, 43.6, 33.3, 29.5, 21.4; IR (ATR, cm^{-1}) 3375, 2932, 1732, 1633, 1445, 1338, 1240, 1156, 1094; HRMS (ESI) calcd for $C_{23}H_{26}N_3O_4S$ $[M+H]^+$ 440.1654; Found: *m/z* 440.1639.

Compound 11: To a solution of 2-iodo-nitrobenzene (288 mg, 1.16 mmol) in dry THF (3 mL) was added PhMgCl (2 M in toluene, 0.607 mL, 1.22 mmol) at −40 °C, and the mixture was stirred at −40 °C for 15 min. The red mixture was then added the solution **5b** (200 mg, 0.526 mmol) in THF (3 mL) at −40 °C and stirred at room temperature for 30 min. The reaction mixture was then quenched with satd. aq. NH_4Cl, extracted with EtOAc, washed with water and brine, dried over Na_2SO_4. After concentration under reduced pressure, purification by flash column chromatography on silica gel (20% EtOAc/hexane) gave **11** (209 mg, 79 %, a 1:1 diastereomeric mixture) as a pale yellow amorphous: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (0.5 H, br s), 8.28 (0.5 H, br s), 7.99-7.97 (1H, m), 7.66-7.58 (3H, m), 7.54-7.47 (1H, m), 7.28-7.27 (1H, m), 7.20-7.07 (4H, m), 6.85-6.83 (1H, m), 6.49-6.47 (1H, m), 6.07-6.04 (1H, m), 5.82-5.66 (1H, m), 5.13-5.08 (1H, m), 4.74 (0.5 H, d, *J* = 17.2 Hz), 4.63 (0.5 H, d, *J* = 17.2 Hz), 3.94-3.91 (1H, m), 3.54-3.49 (2H, m), 3.10-3.07 (1H, m), 2.74-2.66 (1H, m), 2.37-2.36 (3H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.6, 134.1, 133.9, 132.3, 129.9, 129.5, 129.3, 129.2, 127.0 (x2), 125.0, 121.6, 121.5, 119.8, 119.2, 119.0, 110.8, 110.0, 109.9, 65.4, 64.1, 43.5, 28.3, 27.6, 21.4; IR (film, cm^{-1}) 3414, 3027, 2942, 1598, 1526,

1445, 1337, 1228, 1156, 1018, 790, 751, 666; HRMS (FAB) calcd for $C_{27}H_{25}N_3O_5S$ $[M]^+$ 503.1515; Found: *m/z* 503.1533.

Compound 5d: To a solution of **11** (201 mg, 0.40 mmol) in $CHCl_3$ (20 mL) was added MnO_2 (696 mg, 8.0 mmol) at room temperature, and the mixture was stirred at 40 °C for 1 h. After the reaction mixture was filtered through a pad of Celite, and concentration under reduced pressure. The crude material was purifed by flash column chromatography on silica gel (40% EtOAc/hexane) to give **5d** (145 mg, 72%) as a yellow amorphous: $[\alpha]_D^{22}$ –59.8 ° (*c* 0.44, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (1H, s), 8.26 (1H, d, *J* = 8.3 Hz), 7.81-7.78 (1H, m), 7.72-7.69 (1H, m), 7.55 (2H, d, *J* = 8.3 Hz), 7.42 (1H, d, *J* = 7.4 Hz), 7.28-7.26 (2H, m), 7.12 (2H, d, *J* = 8.3 Hz), 6.87-6.87 (1H, m), 6.01 (1H, s), 5.77-5.74 (1H, m), 5.15 (1H, d, *J* = 10.3 Hz), 4.71 (1H, d, *J* = 17.5 Hz), 3.78-3.75 (1H, m), 3.48-3.42 (1H, m), 2.77-2.73 (1H, m), 2.49-2.46 (1H, m), 2.34 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.9, 145.2, 143.1, 138.0, 127.8, 127.5, 136.4, 135.2, 124.7, 130.8, 130.3, 129.4, 128.1, 126.8, 126.3, 125.6, 125.0, 123.1, 121.0, 119.5, 111.1, 63.7, 43.0, 29.3, 21.4; IR (film, cm^{-1}) 3346, 3029, 2946, 2861, 1633, 1572, 1525, 1446, 1415, 1343, 1273, 1251, 1156, 1061, 1019, 992, 939, 852, 1019, 992, 939, 852, 789, 752, 704, 668; HRMS (FAB) calcd for $C_{27}H_{24}N_3O_5S$ $[M+H]^+$ 502.1437; Found: *m/z* 502.1454.

Compound 4a: To a solution of **5a** (50 mg, 0.106 mmol) in CH_2Cl_2 (3 mL) was added ^{t}BuOCl (0.018 ml, 0.159 mmol), and the mixture was stirred at room temperature for 1 h. Concentration under reduced pressure gave the crude material, and used the next reaction without purification. To the solution of the residue in EtOH (2 ml) and CH_2Cl_2 (3 mL) was added HCl (1 M in Et_2O, 0.10 ml), and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressureand purified by flash column chromatography on silica gel (20% EtOAc/hexane) to give **4a** (26 mg, 54%) as a colorless oil: $[\alpha]_D^{21}$ –3.9 ° (*c* 1.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.33 (1H, s), 7.51 (2H, d, *J* = 8.0 Hz), 7.23 (1H, t, *J* = 7.7 Hz), 7.16 (2H, d, *J* = 8.3 Hz), 6.93 (1H, d, *J* = 7.7 Hz), 6.85 (1H, d, *J* = 7.7 Hz), 5.77-5.69 (2H, m), 5.21 (1H, d, *J* = 10.2 Hz), 4.85-4.81 (2H, m), 4.09-4.06 (1H, m), 3.92-3.89 (1H, m), 2.51-2.49 (1H, m), 2.36 (3H, s), 1.55-1.50 (1H, m), 1.12 (3H, d, *J* = 6.3 Hz), 1.05 (3H, d, *J* = 6.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5, 167.2, 143.2, 142.2, 137.9, 137.8, 135.1, 129.5, 129.0, 126.9, 126.8, 123.6, 120.4, 109.6, 70.1, 63.2, 59.3, 41.8, 29.7, 21.4, 21.1 (x2); IR (film, cm^{-1}) 3302, 2987, 2939, 1740, 1713, 1617, 1601, 1494, 1459, 1405, 1388, 1375, 1330, 1304, 1266, 1215, 1157, 1122, 1038, 986, 943, 914, 874, 807; HRMS (FAB) calcd for $C_{24}H_{27}N_2O_5S$ $[M+H]^+$ 455.1641; Found: *m/z* 455.1647.

Compound 4c: **4c** was obtained by following the procedure for **4a**: $[\alpha]_D^{21}$ –8.7 ° (*c* 0.46, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.18 (1H, s), 7.45 (2H, t, *J* = 8.0 Hz), 7.21 (1H, t, *J* = 7.7 Hz), 7.15 (2H, t, *J* = 6.4 Hz), 6.98 (1H, d, *J* = 7.7 Hz), 6.87 (1H, d, *J* = 8.0 Hz), 5.89-5.87 (1H, m), 5.67 (1H, br s), 5.22 (1H, d, *J* = 10.5 Hz), 5.06-5.02 (1H, m), 4.25 (1H, t, *J* = 13.6 Hz), 4.03 (1H, d, *J* = 15.8 Hz), 3.02 (3H, s), 2.95 (3H, s), 2.48-2.45 (1H, m), 2.36 (3H, s), 1.38-1.34 (1H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 169.0, 143.1, 142.3, 138.5, 137.7, 134.7, 129.5, 128.7, 127.4, 126.8, 123.5, 119.6, 109.5, 63.4, 60.0 (x2), 57.9, 42.0, 33.5, 31.2, 21.4; IR (film, cm^{-1}) ; 3257, 2942, 2865, 2822, 1729, 1658, 1458, 1330, 1247, 1158, 984, 868, 816, 745, 662, 605, 544, 522, 509, 507; HRMS (FAB) calcd for $C_{23}H_{26}N_3O_5S$ $[M+H]^+$ 456.1593; Found: *m/z* 456.1608.

Compound 4d: **4d** was obtained by following the procedure for **4a**: $[\alpha]_D^{22}$ –59.9 ° (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.01 (1H, d, *J* = 8.0 Hz), 7.91 (1H, s), 7.56-7.50 (4H, m), 7.29-7.28 (1H, m), 7.19 (2H, d, *J* = 8.0 Hz), 7.02 (1H, d, *J* = 7.7 Hz), 6.91 (1H, s), 6.79 (1H, d, *J* = 7.7 Hz), 6.17-6.11 (1H, m), 5.74 (1H, s), 5.18 (1H, d, *J* = 10.3 Hz), 5.00 (1H, d, *J* = 17.2 Hz), 4.03-3.99 (2H, m), 2.68 (1H, d, *J* = 14.6 Hz), 2.38 (3H, s), 1.91-1.85 (1H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.5, 174.3, 146.7, 143.3, 141.4, 141.2, 137.6, 134.9, 133.0, 132.8, 131.0, 129.8, 129.6, 127.2, 126.9, 124.5, 124.3, 124.0, 118.8, 109.5, 69.3, 66.6, 31.4, 21.5, 14.1; IR (film, cm^{-1}) ; 2979, 2913, 1743, 1716, 1541, 1233, 1087, 965, 914, 744; HRMS (FAB) calcd for $C_{27}H_{24}N_3O_6S$ $[M+H]^+$ 518.1386; Found: *m/z* 518.1381.

Compound 13: To a solution of **5b** (40 mg, 0.105 mmol) in CH_2Cl_2 (2 mL) was added ^{t}BuOCl (0.018 ml, 0.158 mmol), and the mixture was stirred at room temperature for 1 h. Concentration under reduced pressure gave the crude material, and used the next reaction without purification. To the solution of the residue in EtOH (2 ml) and CH_2Cl_2 (3 mL) was added HCl (1 M in Et_2O, 0.10 mL), and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel (20% EtOAc/hexane) to give **13** (28 mg, 73 %) as a white solid: $[\alpha]_D^{23}$ –26.0 ° (*c* 0.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.62 (1H, s), 7.54 (2H, d, *J* = 8.0 Hz), 7.17 (3H, t, *J* = 8.3 Hz), 6.90 (1H, d, *J* = 7.7 Hz), 6.81 (1H, d, *J* = 7.7 Hz), 5.82-5.74 (2H, m), 5.31 (1H, t, *J* = 5.2 Hz), 4.76 (1H, t, *J* = 8.7 Hz), 4.20-4.17 (1H, m), 3.55-3.50 (2H, m), 2.36 (3H, s), 2.17-2.15 (1H, m), 1.49-1.44 (1H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.7, 143.2, 140.9, 137.9, 136.9, 134.9, 129.7, 129.5, 128.3, 127.8, 127.0, 126.9, 122.6, 120.4, 109.3, 63.0, 46.1, 44.6, 28.5, 21.4; IR (film, cm^{-1}) 3300, 2946, 2863, 1705, 1617, 1494, 1460, 1404, 1327, 1249, 1196, 1155, 1014, 970, 946, 908, 855, 809, 781, 727, 710, 659; HRMS (FAB) calcd for $C_{20}H_{20}N_2O_3S$ $[M]^+$ 368.1195; Found: *m/z* 368.1195.

Compound 23 (Table 2, entry 5): To a solution of **5d** (12.2 mg, 0.0244 mmol) in CH_2Cl_2 (2 mL) was added ^{t}BuOCl (4.1 μL, 0.037 mmol), and the mixture was stirred at room temperature for 1 h. Concentration under reduced pressure gave the crude material, used the next reaction without purification. To the solution of residue in EtOH (2 mL) was added conc. HCl (1 μL), and the mixture was stirred at room temperature for 30 min. Iron (6.8 mg, 0.122 mmol) and water (0.50 mL) were added to the solution, and the mixture was refluxed for 3 h. After reaction mixture was filtered through a pad of Celite, and concentration under reduced pressure. The residue was purified by flash column chromatography on silica gel (30% EtOAc/hexane) to give **23** (5.4 mg, 47%) as a colorless oil: $[\alpha]_D^{23}$ –32.7 ° (*c* 0.09, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.51 (1H, s), 8.67 (1H, d, *J* = 8.3 Hz), 8.01 (1H, d, *J* = 8.0 Hz), 7.66 (2H, d, *J* = 8.0 Hz), 7.41-7.29 (3H, m), 7.11-7.10 (4H, m), 6.09 (1H, s), 5.90-5.84 (1H, m), 5.20 (1H, d, *J* = 10.3 Hz), 4.76 (1H, d, *J* = 16.9 Hz), 4.14 (1H, d, *J* = 14.0 Hz), 3.70-3.65 (2H, m), 3.39 (1H, d, *J* = 15.8 Hz), 2.31 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.2, 137.8, 137.7, 134.9, 134.2, 133.7, 132.1, 131.1, 129.5, 128.4, 127.8, 127.0, 124.5, 124.1, 123.3, 123.0, 119.6, 116.7, 116.4, 115.2, 115.1, 112.9, 64.1, 43.1, 31.2, 21.4; IR(film, cm^{-1}) 3219, 3153, 3080, 2936, 2855, 1716, 1590, 1493, 1427, 1409, 1377, 1339, 1283, 1157, 1050, 1015, 795, 749, 706, 665; HRMS (ESI) calcd for $C_{27}H_{22}N_3O_3S$ $[M-H]^-$ 468.1387; Found: *m/z* 468.1374.

Compound 21: To a solution of **5d** (30 mg, 0.060 mmol) in CH_2Cl_2 (2 mL) was added ^{t}BuOCl (10 μL, 0.090 mmol), and the mixture was stirred at room temperature for 1 h. Concentration under reduced pressure gave the crude material, used the next reaction without purification. To the solution of residue in EtOH (4 mL) was added conc. HCl (1 μL), and the mixture was stirred at room temperature for 30 min. The reaction mixture was then quenched with water, extracted with EtOAc, washed with water and brine, dried over Na_2SO_4. After concentration under reduced pressure, purification by flash column chromatography on silica gel (40% EtOAc/hexane) gave **21** (31.9 mg, 98 %) as a white amorphous: $[\alpha]_D^{21}$ +42.7 ° (*c* 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.82 (1H, d, *J* = 8.0 Hz), 7.52-7.45 (3H, m), 7.36 (1H, t, *J* = 7.7 Hz), 7.22-7.16 (4H, m), 7.07 (1H, d, *J* = 7.4 Hz), 6.34 (1H, d, *J* = 7.7 Hz), 5.97-5.91 (1H, m), 5.73 (1H, s), 5.09 (1H, d, *J* = 10.6 Hz), 4.90 (1H, d, *J* = 17.2 Hz), 4.33-4.29 (2H, m), 4.10 (3H, td, *J* = 13.1, 5.7 Hz), 2.72-2.70 (1H, m), 2.37 (3H, s), 1.24 (3H, dd, *J*

= 14.5, 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.1, 178.1, 155.6, 147.8, 143.2, 139.0, 137.8, 134.7, 131.9, 131.54, 131.51, 131.3, 130.0, 129.5, 126.90, 128.87, 125.2, 124.4, 119.9, 118.2, 68.3, 66.4, 63.8, 41.5, 29.7, 21.4, 13.7; IR (film, cm^{-1}) 3028, 2938, 2858, 1714, 1695, 1612, 1573, 1532, 1475, 1434, 1342, 1299, 1245, 1224, 1157, 1012, 882, 845, 813, 749, 706, 690, 662; HRMS (ESI) calcd for $C_{29}H_{28}N_3O_6S$ $[M+H]^+$ 546.1693; Found: *m/z* 546.1697.

Compound 22: To a solution of **21** (31.9 mg, 0.0585 mmol) in EtOH (6 mL) and water (1.5 mL) was added iron (65 mg, 1.16 mmol) and NH_4Cl (65 mg, 1.21 mmol, purchased from KANTO Chemicals). The mixture was refluxed for 1 h. The reaction mixture was then quenched with water, extracted with EtOAc, washed with water and brine, dried over Na_2SO_4. After concentration under reduced pressure, purification by flash column chromatography on silica gel (50% EtOAc/hexane) gave **22** (11.9 mg, 43 %) as a white amorphous: $[\alpha]_D^{27}$ +140.7 ° (*c* 0.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.71 (1H, d, *J* = 7.7 Hz), 7.50-7.46 (3H, m), 7.30-7.27 (3H, m), 7.14 (2H, d, *J* = 8.0 Hz), 7.06-7.03 (2H, m), 6.74-6.67 (1H, m), 5.75 (1H, s), 5.35 (1H, d, *J* = 10.6 Hz), 5.21 (1H, d, *J* = 17.2 Hz), 3.89-3.86 (1H, m), 3.46-3.44 (1H, m), 2.42-2.33 (5H, m), 1.72 (1H, t, *J* = 12.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.4, 166.6 148.1, 143.2, 141.7, 137.4, 135.5, 129.6, 129.2, 127.0, 126.6, 126.2, 126.0, 122.3, 120.3, 116.0, 114.6, 85.0, 61.1, 34.5, 28.2, 21.4; IR (film, cm^{-1}) 3150, 3086, 3040, 2960, 2923, 2857, 1702, 1630, 1607, 1570, 1476, 1431, 1285, 1325, 1266, 1232, 1156, 1087, 1019, 990, 910, 875, 813, 741, 668; HRMS (FAB) calcd for $C_{27}H_{24}N_3O_3S$ $[M+H]^+$ 470.1538; Found: *m/z* 470.1545.

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Keywords: communesin • aurantioclavine • oxidative rearrangement • reductive cyclization • 2-ethoxyindolenine

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[17] The synthesis of compound **6** was reported in reference 13.

[18] Imine **8** was a mixture of diastereomers

[19] Several ligands were evaluated, including PPh_3, $PCy_3{\cdot}HBF_4$, NHC and dialkylbiarylphosphine ligands.

[20] Several bases were examined, including Cs_2CO_3, LiHMDS, NaHMDS, KO^tBu and NaO^tBu.

[21] The same type of fragmentation was also reported by Trost and co-workers: see ref. 3d.

[22] A related side product was also reported by Westwood *et al.*: see N. Voûte, D. Philp, A. M. Z. Slawin, N. J. Westwood, *Org. Biomol. Chem.* **2010**, *8*, 442.

[23] The epimerization of C11 would give an enantiomer of communesins. For synthesis of a natural enantiomer, epimerization of C7 and C2 would be required.

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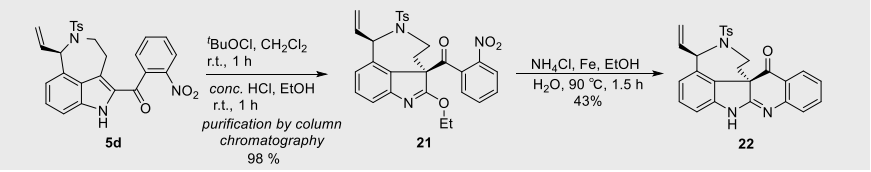

The construction of the pentacyclic skeleton of communesins has been investigated via the oxidative rearrangement of aurantioclavine derivatives, which are thought to be biosynthetic intermediates of the communesins. The C7 quaternary carbon center was constructed in a stereoselective manner, whilst the C11 stereocenter required an epimerization step. The isolation of 2-ethoxyindolenine prior to the reduction of the nitro group and cyclization was critical to the success of the

Natural Product Synthesis

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