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# Synthetic Studies towards Communesins: Diastereoselective Oxidative Rearrangement of Aurantioclavine Derivatives

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**Abstract:** Communesins are a class of heptacyclic indole alkaloids that contain two aminal moieties and two contiguous quaternary carbon centers. We have investigated the construction of the pentacyclic skeleton of the communesins by employing the oxidative rearrangement of aurantioclavine derivatives, which are believed to be biosynthetic intermediates of the polycyclic communesin alkaloids. The quaternary C-7 carbon center was constructed in a stereoselective manner, whereas the installation of the C-11 stereocenter requires an epimerization process. The isolation of a 2-ethoxyindolenine prior to the reduction of the nitro group and cyclization steps was critical to the success of this strategy.

## Introduction

Communesins are a class of heptacyclic indole alkaloids that contain two aminal moieties and two contiguous quaternary carbon centers, and they are isolated from a marine fungal strain of the *Penicillium* species (Figure 1).[1,2] These alkaloids show significant cytotoxicity against P388 lymphocytic leukemia cells [communesins A and B: median effective dose ($ED_{50}$) = 3.5 and 0.45 μg $mL^{-1}$, respectively] as well as potent insecticidal activity towards silkworms [communesins B and E: median lethal dose ($LD_{50}$) = 5 and 80 μg $g^{-1}$, respectively]. These molecules have attracted considerable interest as synthetic targets because of their complex structures and significant biological activity.[3] To date, several total syntheses have been reported for the construction of racemic communesins, including those by Qin,[4] Weinreb,[5] Ma,[6a] and Funk.[7] Furthermore, Ma et al.[6b] reported the development of an asymmetric total synthesis of the communesins. Interestingly, Stoltz and co-workers reported that aurantioclavine, 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 by using a unified stereodivergent alkylation approach as well as a biosynthesis-inspired approach from aurantioclavine. On the basis of a series of genetic inactivation studies, Tang et al.[12] confirmed that the communesins can be biosynthesized by the coupling reaction of tryptamine and aurantioclavine.[12]

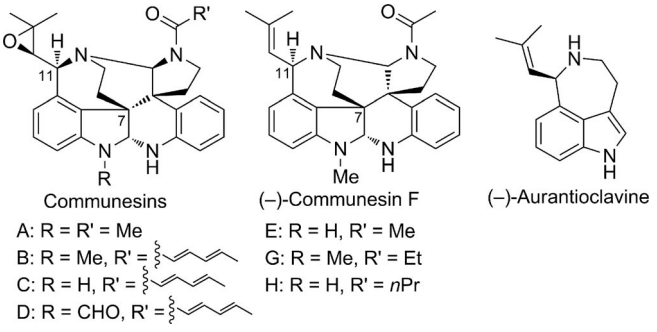


Figure 1. Communesins and (–)-aurantioclavine.

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

It was envisioned that our target could be synthesized from pentacyclic compound **1**, which contains a quaternary C-7 carbon center. Compound **1** could be prepared from **6** by one of two different synthetic routes (Scheme 1). According to the first of these two strategies, pentacyclic skeleton **1** could be constructed by the Pd-catalyzed cyclization[14] of amidine **2**, which is prepared by an $SmI_2$-mediated reductive cyclization[15] of carbodiimide **3** (Scheme 1, route A). $SmI_2$-mediated reductive cyclization reactions of this type represent a powerful and reliable strategy for the synthesis of 2-iminoindolines. The sec-

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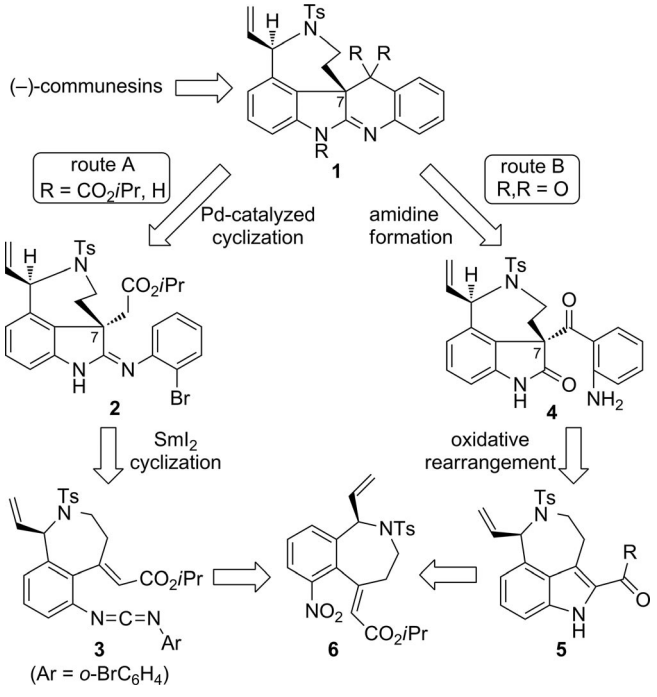
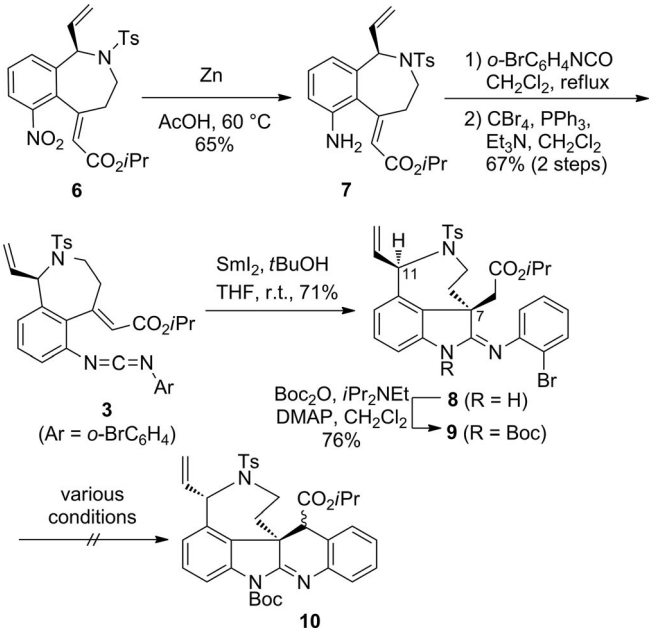
ond potential pathway for the construction of compound **1** involves the oxidative rearrangement of the 2-substituted indole **5**, which has the same structural skeleton as aurantioclavine, to give **4**. The subsequent cyclization of **4** would then give the desired pentacyclic compound **1** (Scheme 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 previously used for the construction of an indole alkaloid.[16] Notably, the two important intermediates **3** and **5** can be derived from common intermediate **6**, which we previously prepared during our synthesis of (–)-aurantioclavine. Herein, we describe our efforts towards the synthesis of pentacyclic skeleton **1** by employing the two described synthetic routes. The isolation of a 2-ethoxyindolenine from the oxidative rearrangement reaction was critical to the success of this strategy, as this step prevented the occurrence of any undesired side reactions.




Scheme 1. Retrosynthesis of the pentacyclic core of the communesins (Ts = *para*-toluenesulfonyl).

## Results and Discussion

Initially, we investigated the synthesis of carbodiimide **3**[13] to explore the feasibility of sequential $SmI_2$-mediated reductive cyclization and Pd-catalyzed cyclization reactions. The reduction of the nitro group of 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 into carbodiimide **3** by using a dehydration reaction that employed $CBr_4$ and $PPh_3$. The amidine core and the desired quaternary carbon center were then successfully constructed by using an $SmI_2$-mediated reductive cyclization reaction.[14] Disappointingly, however, this resulted in the undesired stereochemistry at C-7, which can be explained in terms of the stability differences between the conformers of compound **3** (Figure 2). Conformer **A** is thermodynamically more stable than conformer **B**, because the Ts and vinyl groups are in the axial positions, which minimizes 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 *tert*-butoxycarbonyl (Boc) protection of the indoline nitrogen atom gave compound **9** as a single diastereomer, and both compounds **8** and **9** were screened under an extensive series of Pd-catalyzed conditions in an attempt to effect their cyclization and give the desired pentacyclic compound **10**.[14] However, none of the examined conditions 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. Because the α-position of the ester is congested under the conditions required for Pd-mediated catalysis, it would be difficult for the palladium intermediate,




Scheme 2. Attempted formation of the amidine ring by a Pd-catalyzed cyclization [THF = tetrahydrofuran, DMAP = 4-(dimethylamino)pyridine].

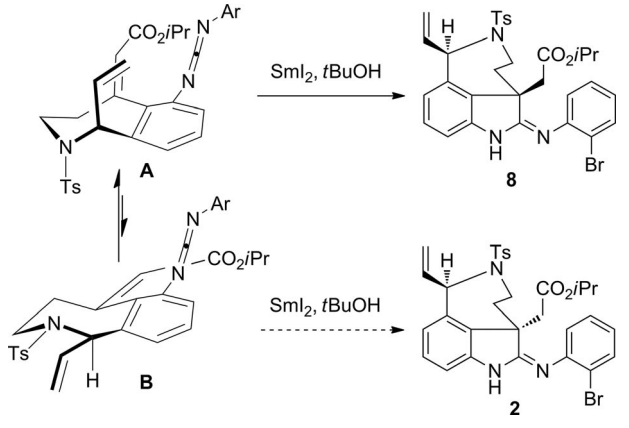
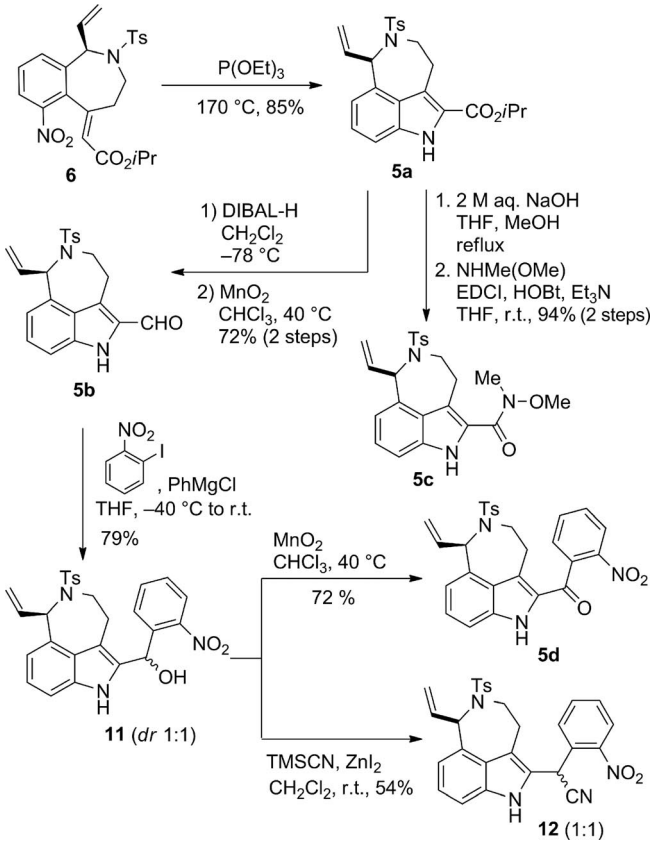



Figure 2. Stereochemistry of $SmI_2$-mediated reductive cyclization of **3**.

which is derived from the oxidative addition of the aryl bromide to $Pd^0$, to react with the enolate. With this in mind, we redirected our focus to the second of the two plans described above (i.e., Scheme 1, route B), in which the fifth ring would be formed by the cyclization of an amidine.[5,8]

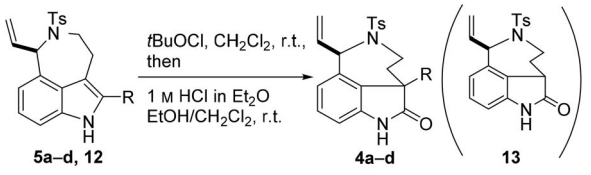
To evaluate the feasibility of the second strategy, we prepared several 2-substituted indoles for the oxidative rearrangement reaction. The treatment of compound **6** with $P(OEt)_3$ at 170 °C gave ester **5a**, which was subjected to a hydrolysis reaction followed by a condensation reaction with *N*-methoxymethylamine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




Scheme 3. Synthesis of substrates **5a**–**5d** and **12** for employment in the oxidative rearrangement {EDCI = *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide, HOBt = *N*-hydroxybenzotriazole, TMSCN = trimethylsilyl cyanide}.

With the series of 2-substituted indoles in hand (i.e., **5a**–**5d** and **12**), we proceeded to investigate each of their oxidative rearrangements to synthesize the corresponding oxindoles, which contain the quaternary C-7 carbon center. Chlorination of ester **5a** with *t*BuOCl followed by 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 into **4c** in 62 % yield (Table 1, Entries 2 and 3). These results are consistent with the results reported by Moody.[16a] Compound **13** was most likely produced by a retro-Claisen-type reaction of **4b** following the oxidative rearrangement. Ketone **5d** smoothly underwent the reaction 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). Thus, these results indicate that the presence of a carbonyl group is important for the stabilization of the transition state of the rearrangement step.

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

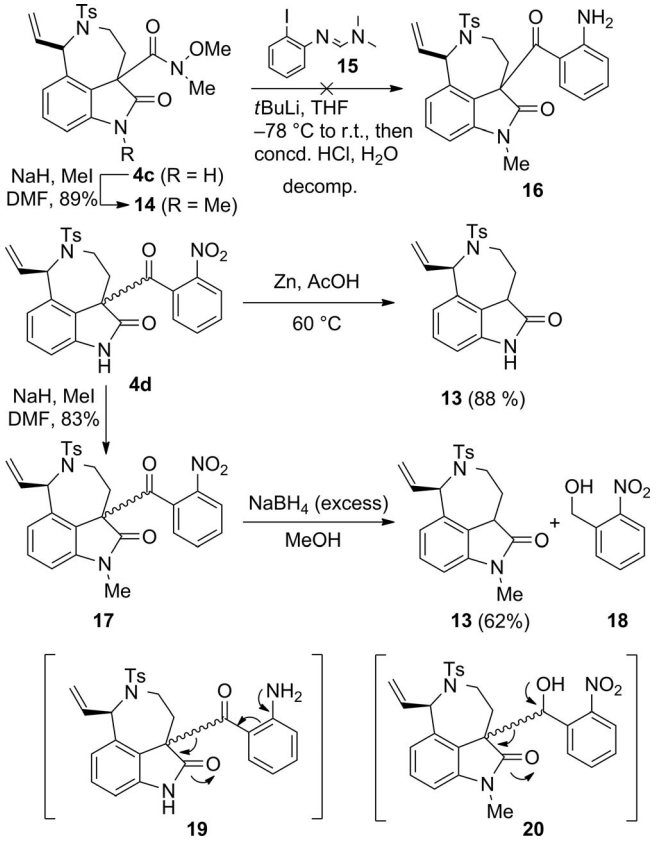



| Entry | Substrate | R | Results[a] |
|---|---|---|---|
| 1 | **5a** | $CO_2iPr$ | **4a** (54%) |
| 2 | **5b** | CHO | **4b** (0%), **13** (73%) |
| 3 | **5c** | CONMe(OMe) | **4c** (62%) |
| 4 | **5d** |  | **4d** (88%) |
| 5 | **12** |  | complex mixture |

[a] Isolated yield.

We then attempted to access a cyclized precursor of our target by using compounds **4c** and **4d** (Scheme 4). The protection of the indole nitrogen atom of **4c** with a methyl group gave compound **14**, which was treated with an in situ generated aryllithium reagent, prepared from iodide **15** and *t*BuLi, in an attempt to prepare compound **16**. This reaction, however, 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** by a similar retro-aldol-type reaction through compound **20**. On the basis of these results, we concluded that the oxindole moiety was the result of an undesired retro-aldol-type reaction, and therefore it would need to be protected prior to the reduction of the nitro and carbonyl groups.

To address the issues described above, we selected 2-alkoxyindolenine, an intermediate of the oxidative rearrangement reaction, as a suitably protected substrate for the reduction of the nitro moiety. Given that 2-ethoxyindolenine **21** was not isolated during the course of our initial evaluations (Table 1), we antici-



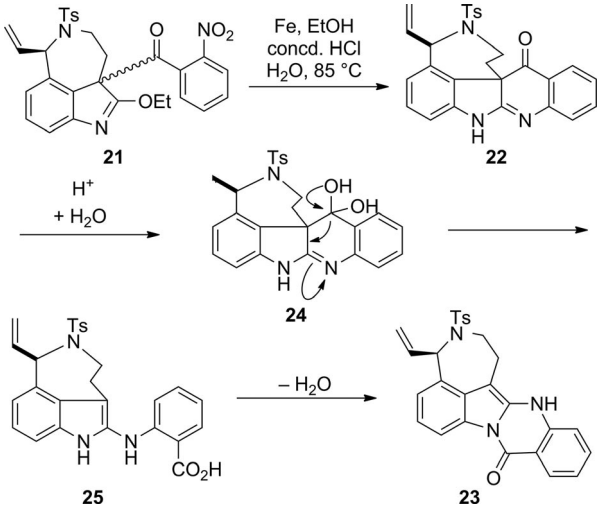

Scheme 4. Attempted derivatization of **4c** and **4d** (DMF = *N*,*N*-dimethylformamide).

pated that this compound would be unstable under the reaction conditions or subsequent purification by column chromatography on silica gel. With this in mind, the reduction of **21** was immediately performed upon its formation by concentrating the reaction mixture without any further purification. Although the reduction of **21** with $SnCl_2$ in toluene gave a complex mixture, the use of Zn in the reaction gave compounds **13** and **23**[22] in 54 and 14 % yield, respectively (Table 2, Entries 1 and 2). When the reduction reaction was conducted in the presence of Fe, a small amount of **23** was produced as part of a complex mixture (Table 2, Entry 3). When 2-propanol was used instead of ethanol to stabilize the intermediate, 2-isopropoxyindolenine **21** was obtained. However, the oxidative rearrangement of this intermediate did not proceed smoothly, and the treatment of this material with Zn gave a complex mixture (Table 2, Entry 4). The reduction reaction was also conducted by using the 2-ethoxyindolenine solution directly from the first step without concentrating the mixture before the reduction. In this case, only compound **23** was afforded in 47 % yield (Table 2, Entry 5). We speculate that byproduct **23** is produced by the formation of pentacyclic skeleton **22** followed by a retro-Claisen-type reaction to form the indoloquinazolinone (Scheme 5). In fact, when a shorter reaction time was used, compound **22** was observed by $^1$H NMR analysis of the crude reaction mixture. Furthermore, it was possible to isolate **22** 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**, we also confirmed that **21** could be readily converted into indoloquinazolinone **23** under acidic conditions (Scheme 5).

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

| Entry | R | Conditions | Results[a] |
|---|---|---|---|
| 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 | *i*Pr | Zn, AcOH, toluene, 85 °C, 2 h | complex mixture |
| 5[b] | Et | Fe, $H_2O$, 90 °C, 3 h | **23** (47 %) |
| 6[b] | Et | Fe, $H_2O$, 90 °C, 45 min | **13** (16 %), **23** (11 %), **21** (28 %), **22** (21 %) |

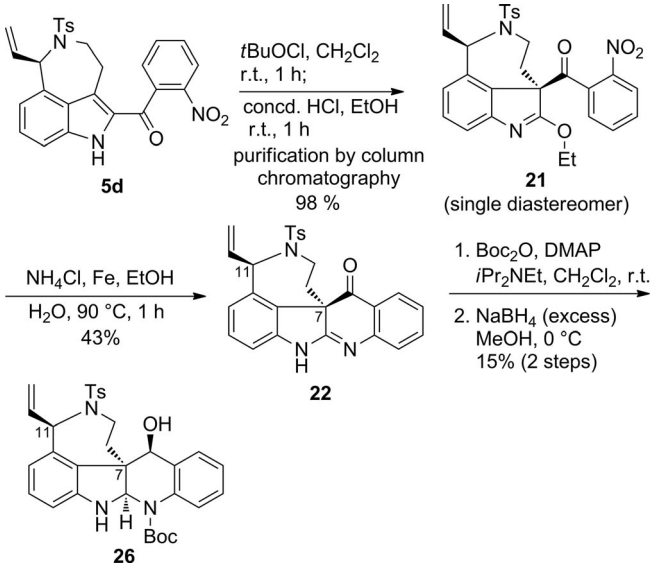
[a] Isolated yield. [b] Concentrated HCl was used in the first step, and the solvent was not evaporated before the reduction.




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

Finally, we successfully isolated 2-ethoxyindolenine **21** in 98 % yield by treating **5d** with *t*BuOCl followed by concentrated 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 pentacyclic compound **22** in 43 % yield without the formation of the undesired indoloquinazoline **23** (Scheme 6). The stereochemistry at C-7 was determined after Boc protection and subsequent reduction of the amidine nitrogen atom to give **26**. The NOESY spectra of **26** reveal the correlation of $H^a$ with $H^b$ and $H^c$ as well as the correlation of $H^d$ with $H^e$ and $H^f$ (Figure 3). These results suggest that the stereochemistry at C-7 is (*R*), and an epimerization of C-11 would be required to construct the communesin core.[23]

On the basis of several previous reports,[16b,16c,16f,16i–16l] the diastereoselectivity of the oxidative rearrangement can be rationalized. The treatment of **5d** with *t*BuOCl gives 3-chloroindolenine **C**, which is thermodynamically more stable than **D** (Scheme 7). The protonation of **C** and formation of chloronium cation **E** is then followed by the addition of EtOH to give intermediate **F**. In this case, the rearrangement occurs through an $S_N1$ rather than an $S_N2$ reaction. The elimination of the chloride ion and the diastereoselective rearrangement of the carboaryl moiety, therefore, proceeds through intermediate **G** to give 2-ethoxyindolenine **21**.




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

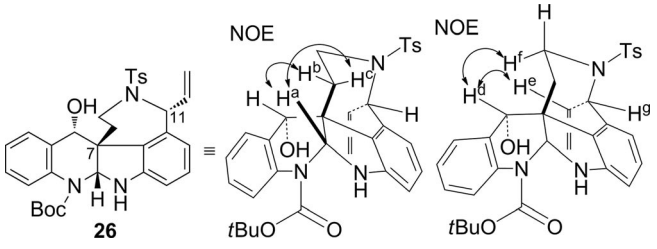
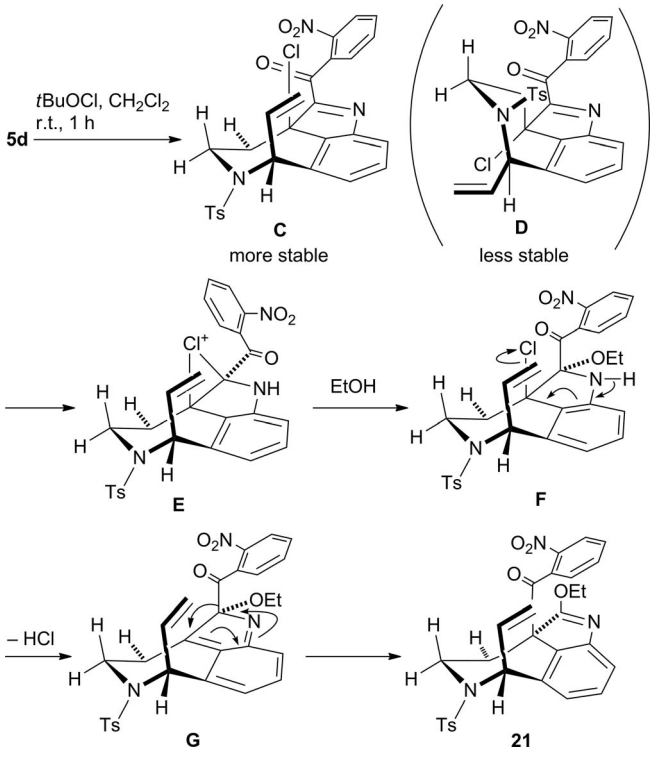



Figure 3. NOESY experiments of compound **26**.




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, which involve: (i) an $SmI_2$-mediated reductive cyclization and Pd-catalyzed cyclization reactions and (ii) an oxidative rearrangement strategy. Although the first of these two strategies was unsuccessful, the desired pentacyclic skeleton was successfully constructed by using the second approach. The quaternary C-7 carbon center was constructed in a stereoselective manner by employing an oxidative rearrangement reaction, but the C-11 stereocenter requires an epimerization step to afford the desired stereochemistry. Finally, the isolation of a 2-ethoxyindolenine prior to the reduction of its nitro group was critical to the success of the cyclization reaction. We are currently investigating the epimerization of the C-11 carbon center with the goal to develop the enantioselective total synthesis of the communesins.

## Experimental Section

**General Methods:** All of the non-aqueous reactions were carried out in dried glassware under a positive pressure of argon. Analytical thin layer chromatography was performed on TLC plates coated with silica gel 60 (Merck). Silica gel column chromatography was performed on Kanto silica gel 60 (particle size 63–210 μm) and Fuji silysia Chromatorex BW-300. The $^1$H NMR spectroscopic data were recorded with a JEOL JNM-ECA 500 instrument (JEOL, Japan) at 500 MHz or a JEOL JNM-AL 400 spectrometer at 400 MHz. Chemical shifts are reported relative to $Me_4Si$ ($\delta$ = 0.00 ppm) in $CDCl_3$. The multiplicities of the signals are described by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br. (broad). The $^{13}$C NMR spectroscopic data were recorded with a JEOL JNM-ECA 500 instrument at 126 MHz or a JEOL JNM-AL 400 spectrometer at 100 MHz. Chemical shifts are reported relative to $CDCl_3$ ($\delta$ = 77.0 ppm). IR spectra were recorded with an FTIR-4100 Fourier transform infrared spectrometer with attenuated total reflectance (JASCO, Japan). Low- and high-resolution mass spectra were recorded with a JEOL JMS-HX/HX 110A mass spectrometer for FAB-MS and a Shimadzu liquid chromatography (LC)–MS-ion trap (IT)-TOF (Shimadzu, Japan) for ESI-MS. Anhydrous $CH_2Cl_2$, THF, methanol, and ethanol were purchased from Kanto Chemical Co., Aldrich, and Wako chemicals. The reagents and materials 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 the residue was purified by flash column chromatography on 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, $CDCl_3$): $\delta$ = 9.04 (br. s, 1 H), 7.69 (d, $J$ = 8.3 Hz, 2 H), 7.27–7.26 (m, 1 H), 7.20 (t, $J$ = 7.7 Hz, 1 H), 7.15 (d, $J$ = 8.0 Hz, 2 H), 6.84 (d, $J$ = 7.2 Hz, 1 H), 6.04 (s, 1 H), 5.77 (ddd, $J$ = 17.1, 10.4, 4.5 Hz, 1 H), 5.30–5.25 (m, 1 H), 5.13 (d, $J$ = 10.3 Hz, 1 H), 4.68 (d, $J$ = 17.3 Hz, 1 H), 4.05–4.03 (m, 1 H), 3.60–3.54 (m, 2 H), 3.44–3.37 (m, 1 H), 2.34 (s, 3 H), 1.39 (d, $J$ = 2.6 Hz, 3 H), 1.38 (d, $J$ = 2.6 Hz, 3 H) ppm. $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ = 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 (2 ×), 21.3 ppm. IR [attenuated total reflectance (ATR)]: $\tilde{\nu}$ = 3344, 2980, 1693, 1452, 1338, 1248,

1156, 1094, 916, 751 $cm^{-1}$. HRMS (ESI): calcd. for $C_{24}H_{27}N_2O_4S$ $[M + H]^+$ 439.1686; found 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 a saturated aqueous solution of Na/K tartrate and stirred vigorously at room temperature for 1 h. The mixture was extracted with EtOAc, and the organic layer was washed with brine and dried with $Na_2SO_4$. Concentration under reduced pressure gave the crude alcohol, which was used in the next step without further 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. The reaction mixture was then filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (30 % EtOAc/hexane) to give **5b** (124 mg, 72 %, 2 steps) as a white amorphous substance; $[\alpha]_D^{22} = -42.8$ ($c = 0.66$, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 9.94 (s, 1 H), 8.94 (br. s, 1 H), 7.69 (d, $J$ = 6.9 Hz, 2 H), 7.30–7.28 (m, 2 H), 7.19 (d, $J$ = 7.4 Hz, 2 H), 6.90–6.89 (m, 1 H), 6.06 (br. s, 1 H), 5.79–5.75 (m, 1 H), 5.16 (d, $J$ = 10.3 Hz, 1 H), 4.67 (d, $J$ = 17.2 Hz, 1 H), 4.11–4.08 (m, 1 H), 3.65 (td, $J$ = 10.2, 5.1 Hz, 1 H), 3.53–3.49 (m, 2 H), 2.37 (s, 3 H) ppm. $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ = 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 ppm. IR (film): $\tilde{\nu}$ = 3317, 2981, 2918, 1649, 1574, 1535, 1460, 1369, 1341, 1278, 1236, 1158, 1092, 1019, 974, 915, 876, 755, 736, 691, 667 $cm^{-1}$. HRMS (FAB): calcd. for $C_{21}H_{21}N_2O_3S$ $[M + H]^+$ 381.1273; found 381.1272.

**Compound 5c:** To a solution of **5a** (150 mg, 0.379 mmol) in MeOH (4 mL) and THF (4 mL) was added NaOH (2 M aqueous solution, 4 mL). The mixture was heated at reflux for 1 h and then concentrated under reduced pressure until the THF and MeOH were removed. The residue was acidified with HCl (2 M aqueous solution, 4 mL), and the resulting mixture was extracted with EtOAc. The organic layer was then dried with $Na_2SO_4$ and concentrated under reduced pressure to give the crude carboxylic acid as a white solid. To a solution of the crude carboxylic acid in THF (8 mL) were added NHMe(OMe) (56 mg, 0.568 mmol), EDCI (109 mg, 0.568 mmol), HOBt (77 mg, 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 and then concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (30 % EtOAc/hexane) to give **5c** (156 mg, 94 %, 2 steps) as a white amorphous substance; $[\alpha]_D^{22} = -39.4$ ($c = 0.27$, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 9.19 (br. s, 1 H), 7.68 (d, $J$ = 8.3 Hz, 2 H), 7.26–7.21 (m, 2 H), 7.14 (d, $J$ = 8.0 Hz, 2 H), 6.88 (d, $J$ = 6.9 Hz, 1 H), 6.09 (s, 1 H), 5.84–5.81 (m, 1 H), 5.14 (d, $J$ = 10.3 Hz, 1 H), 4.71 (d, $J$ = 16.9 Hz, 1 H), 4.01 (d, $J$ = 14.9 Hz, 1 H), 3.68 (s, 3 H), 3.63–3.53 (m, 2 H), 3.41–3.34 (m, 4 H), 2.34 (s, 3 H) ppm. $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ = 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 ppm. IR (ATR): $\tilde{\nu}$ = 3375, 2932, 1732, 1633, 1445, 1338, 1240, 1156, 1094 $cm^{-1}$. HRMS (ESI): calcd. for $C_{23}H_{26}N_3O_4S$ $[M + H]^+$ 440.1654; found 440.1639.

**Compound 11:** To a solution of 1-iodo-2-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. To the red mixture was then added a solution **5b** (200 mg, 0.526 mmol) in THF (3 mL) at –40 °C, and the resulting mixture was stirred at room temperature for 30 min and then quenched with a saturated aqueous solution of $NH_4Cl$. The mixture was extracted with EtOAc, and the organic layer was washed with water and brine, dried with $Na_2SO_4$, and concentrated under reduced pressure. Purification of the crude residue by flash column chromatography on silica gel (20 % EtOAc/hexane) gave **11** (209 mg, 79 %, as a 1:1 diastereomeric mixture) as a pale yellow amorphous substance. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 8.67 (br. s, 0.5 H), 8.28 (br. s, 0.5 H), 7.99–7.97 (m, 1 H), 7.66–7.58 (m, 3 H), 7.54–7.47 (m, 1 H), 7.28–7.27 (m, 1 H), 7.20–7.07 (m, 4 H), 6.85–6.83 (m, 1 H), 6.49–6.47 (m, 1 H), 6.07–6.04 (m, 1 H), 5.82–5.66 (m, 1 H), 5.13–5.08 (m, 1 H), 4.74 (d, $J$ = 17.2 Hz, 0.5 H), 4.63 (d, $J$ = 17.2 Hz, 0.5 H), 3.94–3.91 (m, 1 H), 3.54–3.49 (m, 2 H), 3.10–3.07 (m, 1 H), 2.74–2.66 (m, 1 H), 2.37–2.36 (m, 3 H) ppm. $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ = 137.6, 134.1, 133.9, 132.3, 129.9, 129.5, 129.3, 129.2, 127.0 (2 ×), 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 ppm. IR (film): $\tilde{\nu}$ = 3414, 3027, 2942, 1598, 1526, 1445, 1337, 1228, 1156, 1018, 790, 751, 666 $cm^{-1}$. HRMS (FAB): calcd. for $C_{27}H_{25}N_3O_5S$ $[M]^+$ 503.1515; found 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. The reaction mixture was then filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel (40 % EtOAc/hexane) to give **5d** (145 mg, 72 %) as a yellow amorphous substance; $[\alpha]_D^{22} = -59.8$ ($c = 0.44$, $CHCl_3$). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 9.16 (s, 1 H), 8.26 (d, $J$ = 8.3 Hz, 1 H), 7.81–7.78 (m, 1 H), 7.72–7.69 (m, 1 H), 7.55 (d, $J$ = 8.3 Hz, 2 H), 7.42 (d, $J$ = 7.4 Hz, 1 H), 7.28–7.26 (m, 2 H), 7.12 (d, $J$ = 8.3 Hz, 2 H), 6.87–6.87 (m, 1 H), 6.01 (s, 1 H), 5.77–5.74 (m, 1 H), 5.15 (d, $J$ = 10.3 Hz, 1 H), 4.71 (d, $J$ = 17.5 Hz, 1 H), 3.78–3.75 (m, 1 H), 3.48–3.42 (m, 1 H), 2.77–2.73 (m, 1 H), 2.49–2.46 (m, 1 H), 2.34 (s, 3 H) ppm. $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ = 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 ppm. IR (film): $\tilde{\nu}$ = 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 $cm^{-1}$. HRMS (FAB): calcd. for $C_{27}H_{24}N_3O_5S$ $[M + H]^+$ 502.1437; found 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 and then concentrated under reduced pressure. The crude material was used in the next step without further purification. To the solution of the crude 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 and then concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (20 % EtOAc/hexane) gave **4a** (26 mg, 54 %) as a colorless oil; $[\alpha]_D^{21} = -3.9$ ($c$ = 1.28, $CHCl_3$). $^1H$ NMR ($CDCl_3$): $\delta$ = 8.33 (s, 1 H), 7.51 (d, $J$ = 8.0 Hz, 2 H), 7.23 (t, $J$ = 7.7 Hz, 1 H), 7.16 (d, $J$ = 8.3 Hz, 2 H), 6.93 (d, $J$ = 7.7 Hz, 1 H), 6.85 (d, $J$ = 7.7 Hz, 1 H), 5.77–5.69 (m, 2 H), 5.21 (d, $J$ = 10.2 Hz, 1 H), 4.85–4.81 (m, 2 H), 4.09–4.06 (m, 1 H), 3.92–3.89 (m, 1 H), 2.51–2.49 (m, 1 H), 2.36 (s, 3 H), 1.55–1.50 (m, 1 H), 1.12 (d, $J$ = 6.3 Hz, 3 H), 1.05 (d, $J$ = 6.3 Hz, 3 H) ppm. $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ = 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 (2 ×) ppm. IR (film): $\tilde{\nu}$ = 3302, 2987, 2939, 1740, 1713, 1617, 1601, 1494, 1459, 1405, 1388, 1375, 1330, 1304, 1266, 1215, 1157, 1122, 1038, 986, 943, 914, 874, 807 $cm^{-1}$. HRMS (FAB): calcd. for $C_{24}H_{27}N_2O_5S$ $[M + H]^+$ 455.1641; found 455.1647.

**Compound 4c:** Compound **4c** was obtained according to the procedure for **4a**. $[\alpha]_D^{21} = -8.7$ ($c = 0.46$, $CHCl_3$). $^1H$ NMR ($CDCl_3$): $\delta$ = 9.18 (s, 1 H), 7.45 (t, $J$ = 8.0 Hz, 2 H), 7.21 (t, $J$ = 7.7 Hz, 1 H), 7.15

(t, $J$ = 6.4 Hz, 2 H), 6.98 (d, $J$ = 7.7 Hz, 1 H), 6.87 (d, $J$ = 8.0 Hz, 1 H), 5.89–5.87 (m, 1 H), 5.67 (br. s, 1 H), 5.22 (d, $J$ = 10.5 Hz, 1 H), 5.06–5.02 (m, 1 H), 4.25 (t, $J$ = 13.6 Hz, 1 H), 4.03 (d, $J$ = 15.8 Hz, 1 H), 3.02 (s, 3 H), 2.95 (s, 3 H), 2.48–2.45 (m, 1 H), 2.36 (s, 3 H), 1.38–1.34 (m, 1 H) ppm. $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ = 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 (2 ×), 57.9, 42.0, 33.5, 31.2, 21.4 ppm. IR (film): $\tilde{\nu}$ = 3257, 2942, 2865, 2822, 1729, 1658, 1458, 1330, 1247, 1158, 984, 868, 816, 745, 662, 605, 544, 522, 509, 507 cm$^{-1}$. HRMS (FAB): calcd. for $C_{23}H_{26}N_3O_5S$ $[M + H]^+$ 456.1593; found 456.1608.

**Compound 4d:** Compound **4d** was obtained according to the procedure for **4a**. $[\alpha]_D^{22}$ = –59.9 ($c$ = 1.03, $CHCl_3$). $^1$H NMR ($CDCl_3$): $\delta$ = 8.01 (d, $J$ = 8.0 Hz, 1 H), 7.91 (s, 1 H), 7.56–7.50 (m, 4 H), 7.29–7.28 (m, 1 H), 7.19 (d, $J$ = 8.0 Hz, 2 H), 7.02 (d, $J$ = 7.7 Hz, 1 H), 6.91 (s, 1 H), 6.79 (d, $J$ = 7.7 Hz, 1 H), 6.17–6.11 (m, 1 H), 5.74 (s, 1 H), 5.18 (d, $J$ = 10.3 Hz, 1 H), 5.00 (d, $J$ = 17.2 Hz, 1 H), 4.03–3.99 (m, 2 H), 2.68 (d, $J$ = 14.6 Hz, 1 H), 2.38 (s, 3 H), 1.91–1.85 (m, 1 H) ppm. $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ = 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 ppm. IR (film): $\tilde{\nu}$ = 2979, 2913, 1743, 1716, 1541, 1233, 1087, 965, 914, 744 cm$^{-1}$. HRMS (FAB): calcd. for $C_{27}H_{24}N_3O_6S$ $[M + H]^+$ 518.1386; found 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 and then concentrated under reduced pressure. The crude residue was used in the next step without further 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 and then concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (20 % EtOAc/hexane) gave **13** (28 mg, 73 %) as a white solid; $[\alpha]_D^{23}$ = –26.0 ($c$ = 0.10, $CHCl_3$). $^1$H NMR ($CDCl_3$): $\delta$ = 8.62 (s, 1 H), 7.54 (d, $J$ = 8.0 Hz, 2 H), 7.17 (t, $J$ = 8.3 Hz, 3 H), 6.90 (d, $J$ = 7.7 Hz, 1 H), 6.81 (d, $J$ = 7.7 Hz, 1 H), 5.82–5.74 (m, 2 H), 5.31 (t, $J$ = 5.2 Hz, 1 H), 4.76 (t, $J$ = 8.7 Hz, 1 H), 4.20–4.17 (m, 1 H), 3.55–3.50 (m, 2 H), 2.36 (s, 3 H), 2.17–2.15 (m, 1 H), 1.49–1.44 (m, 1 H) ppm. $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ = 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 ppm. IR (film): $\tilde{\nu}$ = 3300, 2946, 2863, 1705, 1617, 1494, 1460, 1404, 1327, 1249, 1196, 1155, 1014, 970, 946, 908, 855, 809, 781, 727, 710, 659 cm$^{-1}$. HRMS (FAB): calcd. for $C_{20}H_{20}N_2O_3S$ $[M]^+$ 368.1195; found 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 and then concentrated under reduced pressure. The crude residue was used in the next step without further purification. To the solution of the residue in EtOH (2 mL) was added concentrated 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 heated at reflux for 3 h. The reaction mixture was then filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude 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 ($CDCl_3$): $\delta$ = 9.51 (s, 1 H), 8.67 (d, $J$ = 8.3 Hz, 1 H), 8.01 (d, $J$ = 8.0 Hz, 1 H), 7.66 (d, $J$ = 8.0 Hz, 2 H), 7.41–7.29 (m, 3 H), 7.11–7.10 (m, 4 H), 6.09 (s, 1 H), 5.90–5.84 (m, 1 H), 5.20 (d, $J$ = 10.3 Hz, 1 H), 4.76 (d, $J$ = 16.9 Hz, 1 H), 4.14 (d, $J$ = 14.0 Hz, 1 H), 3.70–3.65 (m, 2 H), 3.39 (d, $J$ = 15.8 Hz, 1 H), 2.31 (s, 3 H) ppm. $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ = 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 ppm. IR (film): $\tilde{\nu}$ = 3219, 3153, 3080, 2936, 2855, 1716, 1590, 1493, 1427, 1409, 1377, 1339, 1283, 1157, 1050, 1015, 795, 749, 706, 665 cm$^{-1}$. HRMS (ESI): calcd. for $C_{27}H_{22}N_3O_3S$ $[M - H]^-$ 468.1387; found 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 and then concentrated under reduced pressure. The crude residue was used in the next step without further purification. To the solution of the residue in EtOH (4 mL) was added concentrated HCl (1 µL), and the mixture was stirred at room temperature for 30 min and then quenched with water. The mixture was extracted with EtOAc, and the organic layer washed with water and brine, dried with $Na_2SO_4$, and concentrated under reduced pressure. Purification of the crude residue by flash column chromatography on silica gel (40 % EtOAc/hexane) gave **21** (31.9 mg, 98 %) as a white amorphous substance; $[\alpha]_D^{21}$ = +42.7 ($c$ = 0.51, $CHCl_3$). $^1$H NMR ($CDCl_3$): $\delta$ = 7.82 (d, $J$ = 8.0 Hz, 1 H), 7.52–7.45 (m, 3 H), 7.36 (t, $J$ = 7.7 Hz, 1 H), 7.22–7.16 (m, 4 H), 7.07 (d, $J$ = 7.4 Hz, 1 H), 6.34 (d, $J$ = 7.7 Hz, 1 H), 5.97–5.91 (m, 1 H), 5.73 (s, 1 H), 5.09 (d, $J$ = 10.6 Hz, 1 H), 4.90 (d, $J$ = 17.2 Hz, 1 H), 4.33–4.29 (m, 2 H), 4.10 (td, $J$ = 13.1, 5.7 Hz, 3 H), 2.72–2.70 (m, 1 H), 2.37 (s, 3 H), 1.24 (dd, $J$ = 14.5, 7.3 Hz, 3 H) ppm. $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ = 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 ppm. IR (film): $\tilde{\nu}$ = 3028, 2938, 2858, 1714, 1695, 1612, 1573, 1532, 1475, 1434, 1342, 1299, 1245, 1224, 1157, 1012, 882, 845, 813, 749, 706, 690, 662 cm$^{-1}$. HRMS (ESI): calcd. for $C_{29}H_{28}N_3O_6S$ $[M + H]^+$ 546.1693; found 546.1697.

**Compound 22:** To a solution of **21** (31.9 mg, 0.0585 mmol) in EtOH (6 mL) and water (1.5 mL) were added iron (65 mg, 1.16 mmol) and $NH_4Cl$ (65 mg, 1.21 mmol, purchased from Kanto Chemicals). The mixture was heated at reflux for 1 h and then quenched with water. The mixture was extracted with EtOAc, and the organic layer washed with water and brine, dried with $Na_2SO_4$, and concentrated under reduced pressure. Purification of the crude residue by flash column chromatography on silica gel (50 % EtOAc/hexane) gave **22** (11.9 mg, 43 %) as a white amorphous substance; $[\alpha]_D^{27}$ = +140.7 ($c$ = 0.12, $CHCl_3$). $^1$H NMR ($CDCl_3$): $\delta$ = 7.71 (d, $J$ = 7.7 Hz, 1 H), 7.50–7.46 (m, 3 H), 7.30–7.27 (m, 3 H), 7.14 (d, $J$ = 8.0 Hz, 2 H), 7.06–7.03 (m, 2 H), 6.74–6.67 (m, 1 H), 5.75 (s, 1 H), 5.35 (d, $J$ = 10.6 Hz, 1 H), 5.21 (d, $J$ = 17.2 Hz, 1 H), 3.89–3.86 (m, 1 H), 3.46–3.44 (m, 1 H), 2.42–2.33 (m, 5 H), 1.72 (t, $J$ = 12.6 Hz, 1 H) ppm. $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ = 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 ppm. IR (film): $\tilde{\nu}$ = 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 cm$^{-1}$. HRMS (FAB): calcd. for $C_{27}H_{24}N_3O_3S$ $[M + H]^+$ 470.1538; found 470.1545.

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**Keywords:** Alkaloids · Heterocycles · Rearrangement · Cyclization · Diastereoselectivity

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[20] Several bases were examined including $Cs_2CO_3$, lithium hexamethyldisilazide (LiHMDS), NaHMDS, KO*t*Bu, and NaO*t*Bu.

[21] The same type of fragmentation was also reported by Trost and coworkers. For details, see ref.[3d]

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[23] Epimerization at C-11 gives an enantiomer of the communesins. For the synthesis of a natural enantiomer, epimerization at C-7 and C-2 is required.

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