

Published on Web 09/02/2010

Total Synthesis and Absolute Stereochemical Assignment of (–)-Communesin F

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Abstract: A concise asymmetric total synthesis of (–)-communesin F (~6% overall yield in the longest linear sequence of 19 steps) is described. It features an unprecedented intramolecular oxidative coupling strategy for the elaboration of the requisite spiro-fused indoline moiety. Other notable elements are the use of TBS-protected (*S*)-phenylglycinol as a chiral auxiliary to induce the asymmetric formation of the spiro-fused indoline part, the mesylate-mediated formation of its G ring, and the introduction of the A ring at the final stage via intramolecular Staudinger reaction. This intramolecular Staudinger reaction proceeded smoothly at 80 °C, providing an additional example illustrating that twisted amides are more reactive than simple amides. Along with the total synthesis, we were able to assign the absolute configuration of natural communesin F as 6R,7R,8R,9S,11R.

The indole alkaloid communesin F (1, Figure 1) belongs to a growing family of natural products isolated from a marine fungal strain of *Penicillium* species that now contains eight members (communesins A-H).^{1,2} Preliminary biological evaluation has revealed that these alkaloids possess significant cytotoxicity and insecticidal activity.¹ Their interesting biological activities and unique structures have attracted considerable attention from synthetic chemists worldwide.^{2–5} This campaign has afforded several elegant protocols for assembling the core structure of these indole alkaloids.³ However, only two completed total syntheses have been disclosed,^{4,5} implying that there are some challenges in the total syntheses of these natural products. Herein we report the first asymmetric total synthesis of (–)-communesin F, which allows the establishment of the absolute configuration of these natural products.

As depicted in Figure 1, we expected that the target molecule 1 could be synthesized from diol 2 via formation of the G and A rings. The diol 2 could be obtained from pentacyclic compound 3 via two carbon-chain elongation reactions. Since a nucleophilic cyclization of indoline 4 could deliver the amide 3, we planned to assemble the requisite spiro-fused indoline 4 through an intramolecular oxidative coupling reaction of dianion 5 generated from 3-substituted indole 6.

During the past few years, Baran and co-workers⁶ have demonstrated that the direct intermolecular coupling of some carbonyl compounds with unfunctionalized indoles and pyrroles can be accomplished by deprotonation and subsequent oxidation. Inspired by these achievements, we decided to explore the possibility of constructing spiro-fused indolines via an intramolecular oxidative coupling of 3-substituted indoles bearing an activated methylene moiety. If this transformation were to succeed, we would have a powerful approach for accessing a number of indole alkaloids that contain spiro-fused indoline core structures.



Figure 1. Retrosynthetic analysis of (-)-communesin F.

With this idea in mind, we conducted a model reaction by treatment of **7a** (X = H) with LiHMDS (Scheme 1). To our delight, after the resultant dianion was trapped with iodine, the desired indoline **8a** was isolated in 38% yield. We next checked Bocprotected aniline **7b** and were disappointed by our inability to find any cyclization products. Further evaluation indicated that nitrocontaining amide **7c** is a suitable substrate, as spiro-fused indoline **8c** could be obtained in 83% yield as a diastereomeric mixture with a ratio of 2:1. These differences in reactivity indicated that the pK_a values of the activated methylene units might have a crucial influence on the oxidative coupling step.

Scheme 1



On the basis of the success of the model reactions, we started our total synthesis of communesin F. As shown in Scheme 2, oxidation of 4-bromotryptophol (9) followed by reductive amination with TBS-protected (*S*)-phenylglycinol afforded secondary amine **10**, which was condensed with 2-(2-nitrophenyl)acetic acid with the assistance of BOPCl to provide the desired amide **6**. As we expected, oxidative coupling of **6** proceeded well under the established reaction conditions, delivering spiro-fused indoline **4** as a diastereomeric mixture. After reduction of the nitro group in **4** with iron powder and ammonium chloride, the resultant amine attacked the imine part spontaneously to afford a pentacyclic intermediate, which was subjected to selective methylation to afford aminal **11a** in 50% overall yield together with its diastereomer **11b** in 16% yield. This result indicated that the chiral auxiliary part could lead to reasonable asymmetric induction in the oxidative coupling step.

Scheme 2^a



^{*a*} Conditions: (a) IBX, DMSO; (b) (*S*)-*O*-TBS-phenylglycinol, NaB-H(OAc)₃; (c) 2-(2-nitrophenyl)acetic acid, BOPCl, Et₃N, CH₂Cl₂, 0 °C to rt; (d) LiHMDS, THF, -78 °C followed by iodine, -78 °C to rt; (e) Fe, NH₄Cl, *t*BuOH, H₂O, reflux; (f) KO*t*Bu, MeI, THF, 0 °C.

Protection of **11a** with $(Boc)_2O$ produced **3** (Scheme 3), which was subjected to allylation (KOtBu then allyl iodide) and subsequent desilylation with TBAF to deliver alcohol **12** as a single isomer. A similar stereochemical outcome in the allylation step was observed in Weinreb's synthesis of communesin F.⁵ X-ray structural analysis of **12** revealed that this heterocycle has a 6*S*,7*R*,8*R* configuration (see the Supporting Information for detailed studies), which would allow us to establish the absolute configuration of natural communesin F. Next, removal of the chiral auxiliary in **12** was successively conducted using Ennis' elimination/hydrolysis method⁷ to give amide **13**. Oxidative cleavage of the C–C double bond in **13** with NaIO₄/ K₂OSO₄(H₂O)₂ followed by reduction with NaBH₄ afforded alcohol **14** in 95% yield. Aryl bromide **14** was coupled with 2-methyl-3-buten-2-ol under modified Heck reaction conditions to afford the desired diol **2** (80% yield based on 17% recovery of **14**).^{4,8}

With allyl alcohol 2 in hand, we continued our synthesis by formation of the G and A rings of communesin F. In their previous reports, both Qin⁴ and Weinreb⁵ chose to construct the B ring at the final stage. This strategy would have required opening of the existing B ring and subsequent operations, which would have decreased the synthetic efficiency considerably. We thought that it would be possible to synthesize the target molecule more efficiently if formation of the A ring could be achieved at the final stage. Accordingly, conversion of 2 to the corresponding azide was carried



^{*a*} Conditions: (a) KHMDS, (Boc)₂O, THF, 0 °C; (b) KOtBu, allyl iodide, ether, rt; (c) TBAF, THF; (d) LiOH·H₂O, DMSO, 100 °C; (e) HCl, THF, 60 °C; (f) NaIO₄, K₂OSO₄(H₂O)₂, NMO, THF, H₂O; (g) NaBH₄, MeOH; (h) Pd(OAc)₂, P(*o*-Tol)₃, PMP, *n*Bu₄NBr, 3:2 2-methyl-3-buten-2-ol/DMF, microwave, 140 °C, 20 min; (i) MsCl, Et₃N, CH₂Cl₂, 0 °C; (j) NaN₃, *n*Bu₄NBr, DMF, 90 °C; (k) P(*n*Bu)₃, toluene, 80 °C; (l) NaBH₄, HOAc, Ac₂O; (m) CF₃CO₂H, CH₂Cl₂.

out. To our surprise, treatment of 2 with mesyl chloride and triethylamine not only resulted in the mesylation but also formation of the G ring, thereby providing hexacyclic mesylate 15 in 63% yield. This mesylate was treated with sodium azide in DMF at 90 °C to give azide 16. We then shifted our attention to the formation of the amidine moiety via an intramolecular Staudinger reaction. A literature survey indicated that intramolecular Staudinger reactions of simple amides require rather high reaction temperatures to afford the cyclic amidines in moderate yields,9 although activated amides proceed smoothly in similar transformations.¹⁰ Indeed, Funk and Fuchs^{11a} were unsuccessful in using this method to construct the amidine unit of perophoramidine, a natural product structurally related to the communesins. This problem forced them to reach the goal by transforming the lactam into the more reactive imidate with Meerwein's reagent.¹¹ We envisioned that the intermediate 16 is a twisted amide in which the carbonyl group should become more reactive because of the loss of conjugation between the amide nitrogen and the C=O π bond,¹² and we thought that this character might offer us an opportunity to obtain the desired cyclic amidine under mild conditions. Gratifyingly, exposure of 16 to tri-n-butylphosphine in toluene at 80 °C delivered amidine 17 in 82% yield (53% overall yield from 2 to 17 was obtained when purification of 15 and 17 was omitted). Finally, reduction of 17 with NaBH₄ followed by cleavage of the Boc group with TFA furnished the target molecule 1. The sign of rotation for our synthetic 1 ($\left[\alpha\right]_{D}^{24.5} = -249.5$ (c 0.30, CHCl₃)) was consistent with that reported for natural communesin F $([\alpha]_D^{20} = -264 (c \ 0.34, CHCl_3))$. Therefore, we could conclude that the absolute configuration of natural communesin F is identical to that of communesins A and B.

In conclusion, we have accomplished the first total synthesis of (-)-communesin F in 19 steps (longest linear sequence from 4-bromotryptophol) in ~6% overall yield. Along with the total synthesis, the absolute configuration of this natural product was established, which will be helpful in solving the remaining stereochemical questions for the other communesins as well as perophoramidine. Our approach for efficiently constructing the G and A rings will be of benefit for the assembly of the other members of the communesin family, while our spiro-fused indoline formation via an intramolecular oxidative coupling will stimulate further applications in the syntheses of related indole alkaloids. Investigations in this direction are being actively pursued in our laboratory, and the results will be disclosed in due course.

Acknowledgment. The authors are grateful to the National Basic Research Program of China (973 Program, Grant 2010CB833200), the Chinese Academy of Sciences, and the National Natural Science Foundation of China (Grants 20632050 and 20921091) for their financial support.

Supporting Information Available: Experimental and spectral data for all new compounds and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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