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Enantioselective synthesis and stereochemical revision of communiols A–C

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Abstract—Enantioselective synthesis of the proposed structure of communiol C, an antibacterial tetrahydrofuran derivative produced by *Podospora communis*, and its stereoisomers revealed that the genuine stereochemistry of communiol C should be 3*R*, 5*R*, and 6*S*. Two other structurally related metabolites of the same microbial origin, communiols A and B, were also synthesized based on the revised stereochemistry.

Communiols A–D (**1**–**4**, Fig. 1) were recently isolated from the culture broth of the coprophilous (dung-colonizing) fungus, *Podospora communis*, by Gloer and co-workers as its metabolites exhibiting significant antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus*.[1] The 2,4-disubstituted tetrahydrofuran substructure incorporated in **1**–**3** is relatively rare as a structural unit of natural products and displays a characteristic difference in substitution pattern from 2,5-disubstituted tetrahydrofurans frequently found in annonaceous acetogenins[2] or ionophores.[3] To the best of our knowledge, the most structurally similar natural product seems to be aureonitol,[4] a fungal metabolite possessing a 2,4-dialkadienyl-substituted tetrahydrofuran framework, although it has an additional hydroxyl substituent at its C3 position. The 3,7-disubstituted 2,8-dioxabicyclo[3.3.0]octane structure contained in communiol D (**4**) is also rare, although some related structural units analogous to but different in substitution and/or oxidation patterns from the bicyclic portion of **4** have been found in many natural products such as clerodane diterpenoids and fungal metabolites.[5] These structural uniqueness of communiols A–D, coupled with their interesting biological activity, prompted us to embark on the synthesis of **1**–**4**. We describe herein, our studies on the enantioselective synthesis of communiols A–C, which led us to the conclusion that the stereochemistry of communiols A–C should be revised.

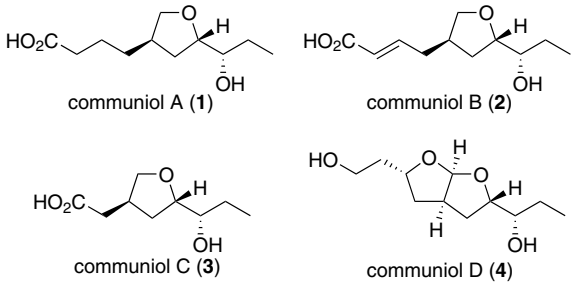

Figure 1. Originally proposed structures for communiols A–D.

Our synthesis of communiol C (**3**), chosen as our first synthetic target due to its structural simplicity, began with the Sharpless asymmetric dihydroxylation[6,7] of known olefinic ester **5**[8,9] using AD-mix-α as the chiral catalyst (Scheme 1). Exposure of the resulting crude product consisting of diol **6** and its lactonization product **7** to acidic conditions brought about complete conversion of **6** into **7**, whose ^{1}H NMR spectrum was in good agreement with that reported for an authentic sample of **7** previously prepared from L-glutamic acid.[10] The absolute stereochemistry of **7** was confirmed by comparison of its specific rotation value ($[\alpha]_D^{22}$ +40.3 (*c* 2.25, CH_2Cl_2)) with the literature value ($[\alpha]_D^{22}$ + 46.0 (*c* 2.0, CH_2Cl_2)),[10] and the enantiomeric excess

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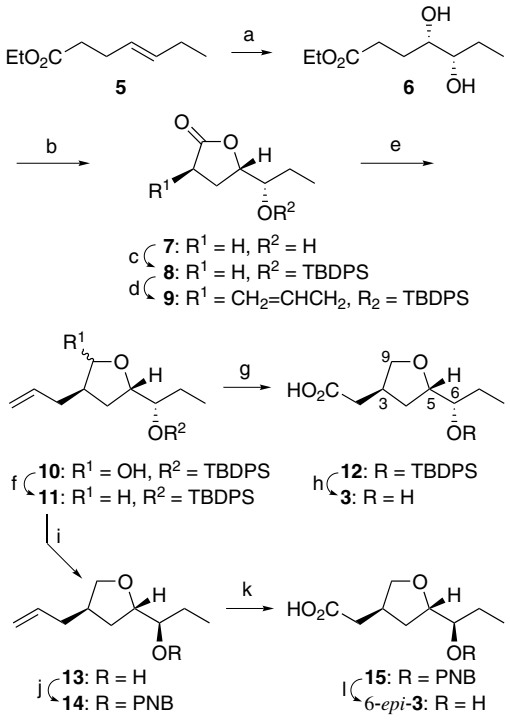
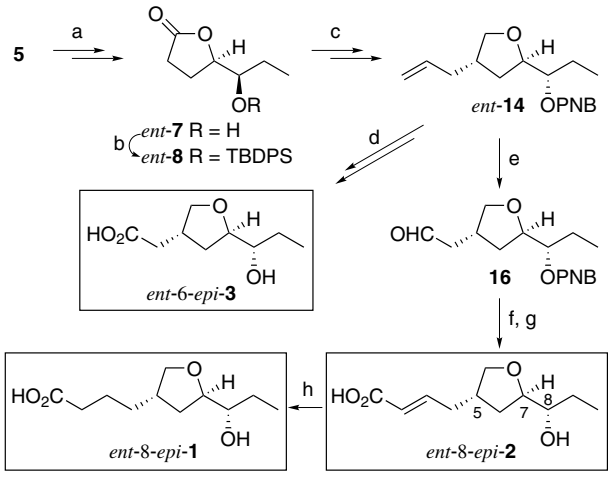


Scheme 1. Synthesis of the originally proposed structure for communiol C (**3**) and its C6-epimer (6-*epi*-**3**). Reagents and conditions: (a) AD-mix-α, $CH_3SO_2NH_2$, *t*-BuOH/H_2O, 0 °C, 12 h; (b) TsOH·H_2O, CH_2Cl_2, rt, 1 h (94%, two steps); (c) TBDPSCl, imidazole, DMF, rt, 21 h (87%); (d) LDA, CH_2=$CHCH_2Br$, THF/HMPA, −78 °C, 30 min (64%); (e) DIBAL, CH_2Cl_2, −78 °C, 30 min; (f) Et_3SiH, BF_3·OEt, CH_2Cl_2, −78 to −5 °C, 8 h (86%, two steps); (g) $RuCl_3$·$(H_2O)_n$, $NaIO_4$, H_2O/CH_3CN/CCl_4, rt, 2 h (63%); (h) aq HF, CH_3CN, rt, 22 h (67%); (i) TBAF, THF, rt, 2 days (66%); (j) DEAD, Ph_3P, *p*-$NO_2C_6H_4CO_2H$, toluene, rt, 2 days (59%); (k) $RuCl_3$·$(H_2O)_n$, $NaIO_4$, H_2O/CH_3CN/CCl_4, rt, 2.5 h; (l) aq K_2CO_3, rt, 24 h (36%, two steps).

of **7** was estimated to be 93.5% by analyzing the ^{1}H NMR spectra of the corresponding (*R*)- and (*S*)-MTPA esters.[11] After protection of the hydroxyl group of **7** as its *t*-butyldiphenylsilyl (TBDPS) ether **8**, the lactone was subjected to well-documented trans-selective alkylation with allyl bromide,[12,13] which afforded a separable 8.3:1 mixture of desired product **9** and the corresponding *cis*-allylation product. When the protective group was changed into *t*-butyldimethylsilyl (TBS), the reaction showed a much lower selectivity of 2.3:1, probably reflecting the smaller steric bulkiness of TBS as compared to TBDPS. The lactone **9** was purified by SiO_2-column chromatography and then reduced with DIBAL to afford lactol **10** as an approximately 3:1 mixture of epimers. Reductive removal of the newly generated hydroxyl group of **10** with triethylsilane in the presence of BF_3·OEt_2[14] proceeded smoothly to give tetrahydrofuran derivative **11**, the double bond of which was then cleaved oxidatively to give carboxylic acid **12**.[15] Finally, deprotection of the TBDPS group with aq HF in acetonitrile completed the synthesis of **3**, the proposed structure of communiol C. Direct comparison of the ^{1}H NMR spectrum of synthetic **3** with that of natural communiol C, however, revealed some clear differences, especially in the chemical shifts for 5-H, 6-H, and 9-H_2. In the synthetic sample **3**, the peaks for 5-H, 6-H, and 9-H_2 appeared at δ 3.85, 3.34, and 4.06/3.49, respectively, while the corresponding peaks of natural communiol C were observed at δ 3.90, 3.68, and 4.09/3.41. In their report on the structural determination of communiols A–D, Gloer and co-workers determined the trans-relative stereochemistry between the C3- and C5-substituents of communiol C by observing some clear diagnostic NOESY correlations, and assigned the absolute configuration at the C6 chiral center to be *S* by analogy with the (*S*)-absolute configuration of communiol A (**1**), which in turn was established unambiguously by the modified Mosher method.[1] The relative stereochemistry between C5 and C6 of communiol C was, however, proposed only on the basis of Born's empirical rule,[16] which has been used for determining the relative stereochemistry between C2 and C1′ stereogenic centers of 2-(1′-hydroxyalkyl)tetrahydrofuran system.[17,18] According to the rule, the C1′ signal is observed at ca. 74 ppm in ^{13}C NMR when the C2/C1′-relative stereochemistry is *threo*, while that of *erythro*-isomer appears at ca. 72 ppm. The observed chemical shift (δ 73.7) for the C6 carbon of natural communiol C led them to propose its C5/C6-relative stereochemistry to be *threo* as represented by structure **3**. To the best of our knowledge, however, Born's rule has not been applied to the determination of the C2/C1′-relative stereochemistry of 2,4-disubstituted tetrahydrofurans like communiols A–C, which made us to suppose that the genuine C5/C6-relative stereochemistry of communiol C might not be *threo*, but *erythro*. Based on this presumption, we synthesized the 5,6-*erythro*-stereoisomer of **3** (i.e., 6-*epi*-**3** in Scheme 1) from intermediate **11** by a four-step sequence consisting of deprotection of the silyl protective group (**11** → **13**), the Mitsunobu inversion of the resulting alcohol to form the corresponding *p*-nitrobenzoate derivative (**13** → **14**),[19] oxidative cleavage of the double bond of **14** to carboxylic acid **15**, and finally, alkaline hydrolysis of the ester functionality of **15** to furnish 6-*epi*-**3**. As expected, the ^{1}H NMR spectrum of 6-*epi*-**3** was exactly the same as that of natural communiol C, which enabled us to establish the relative stereochemistry of communiol C as 3,5-*trans* and 5,6-*erythro*. Comparison of the specific rotation value of 6-*epi*-**3** with that of natural communiol C ($[\alpha]_D^{22}$ +3.6 (*c* 0.24, CH_2Cl_2) and $[\alpha]_D$ −3.4 (*c* 0.142, CH_2Cl_2),[1] respectively) as well as the newly established relative stereochemistry of communiol C led us to the conclusion that Gloer's assignment of the (6*S*)-absolute configuration for natural communiol C was correct, but the genuine structure of communiol C should be revised to *ent*-6-*epi*-**3** (the enantiomer of 6-*epi*-**3**, see Scheme 2).

According to the revised stereochemistry of communiol C, we set about the synthesis of *ent*-6-*epi*-**3** (Scheme 2). By following the same set of reactions as employed for the preparation of **7** except that AD-mix-β, instead of AD-mix-α, was used for the asymmetric dihydroxylation of **5**,[6] olefinic ester **5** was converted into hydroxy lactone *ent*-**7** ($[\alpha]_D^{22}$ −41.3 (*c* 2.25, CH_2Cl_2)), whose enantiomeric excess was determined to be 96% by the same method as used for **7**. Protection of its hydroxyl group as a TBDPS ether gave rise to *ent*-**8** as a white crystalline solid. A single recrystallization of the solid from hexane/EtOAc



Scheme 2. Synthesis of the revised structures for communiols A–C. Reagents and conditions: (a) (i) AD-mix-β, $CH_3SO_2NH_2$, *t*-BuOH/H_2O, 0 °C, 12 h; (ii) TsOH·H_2O, CH_2Cl_2, rt, 1 h (89%, two steps); (b) (i) TBDPSCl, imidazole, DMF, rt, 19 h (quant); (ii) recrystallization from hexane/EtOAc (75%); (c) steps (d)–(f) in Scheme 1 (71%, three steps); (d) steps (i)–(l) in Scheme 1 (41%, four steps); (e) O_3, MeOH, −78 °C, 5 min, then Me_2S, −78 °C to rt, 2 h (85%); (f) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 9 h (82%); (g) aq LiOH, THF, rt, 20 h (95%); (h) H_2, 10% Pd–C, EtOH, rt, 1 h (96%).

yielded enantiomerically pure *ent*-**8** (mp 62.5–63 °C), whose optical integrity was checked by analyzing the ^{1}H NMR spectra of the corresponding (*R*)- and (*S*)-MTPA esters, which in turn were obtained by treatment of the optically enriched silyl ether with TBAF followed by (*R*)- and (*S*)-MTPA-esterifications of the resulting alcohol (*ent*-**7**, $[\alpha]_D^{22}$ −46.8 (*c* 0.24, CH_2Cl_2)). The lactone *ent*-**8** was then converted into *ent*-6-*epi*-**3** via *ent*-**14** by the same seven-step sequence as employed for the synthesis of 6-*epi*-**3**. The ^{1}H and ^{13}C NMR spectra of *ent*-6-*epi*-**3** were identical with those of natural communiol C, and its specific rotation value ($[\alpha]_D^{22}$ −2.7 (*c* 1.155, CH_2Cl_2)) was in good agreement with that of natural communiol C ($[\alpha]_D$ −3.4 (*c* 0.142, CH_2Cl_2))[1] including the minus sign. Based on these results, we concluded that the genuine structure of communiol C should be *ent*-6-*epi*-**3** as depicted in Scheme 2.

Assuming that the structurally related tetrahydrofuran derivatives (communiols A and B) of the same microbial origin should have the same stereochemical arrangement as communiol C, we started the synthesis of (5*S*,7*R*,8*S*)-communiol A (*ent*-8-*epi*-**1**) and (5*S*,7*R*,8*S*)-communiol B (*ent*-8-*epi*-**2**) from *ent*-**14**. Ozonolysis of the double bond of *ent*-**14** gave aldehyde **16**, the chain elongation of which by the Wittig reaction afforded *ent*-8-*epi*-**2** after hydrolysis of the PNB ester group. Catalytic hydrogenation of *ent*-8-*epi*-**2** completed the synthesis of *ent*-8-*epi*-**1**. The ^{1}H and ^{13}C NMR spectra of *ent*-8-*epi*-**1** and *ent*-8-*epi*-**2** were exactly the same as those of natural communiol A and communiol B, respectively, which enabled us to revise the originally proposed 7,8-*threo*-relative stereochemistry of natural communiols A and B to 7,8-*erythro* relationship. Curiously enough, however, the specific rotation values of *ent*-8-*epi*-**1** ($[\alpha]_D^{22}$ +1.3 (*c* 0.22, CH_2Cl_2)) and *ent*-8-*epi*-**2** ($[\alpha]_D^{22}$ +4.7 (*c* 1.0, CH_2Cl_2)) were inconsistent with those of natural communiol A ($[\alpha]_D$ −1.6 (*c* 0.25, CH_2Cl_2)) and natural communiol B ($[\alpha]_D$ −95 (*c* 0.075, CH_2Cl_2)), respectively.[1] At present, we are unable to clearly explain these discrepancies in specific rotation, but small amounts of impurities contained in the synthetic and/or natural samples of communiols A and B might have affected the observed specific rotation values.

In summary, the enantioselective total syntheses of the originally proposed structure (**3**) for communiol C, its C6-epimer (6-*epi*-**3**), and (3*R*,5*R*,6*S*)-stereoisomer (*ent*-6-*epi*-**3**) were accomplished starting from known olefinic ester **5** by using the Sharpless asymmetric dihydroxylation as the source of chirality, which revealed that the genuine stereochemistry of communiol C should be represented by *ent*-6-*epi*-**3**. Based on this newly established stereochemistry of communiol C as well as the assumption that two other structurally related metabolites of the same microbial origin, communiols A and B, should share the same stereochemical arrangement as communiol C, *ent*-8-*epi*-**1** and *ent*-8-*epi*-**2** were synthesized as highly probable candidates for the genuine structures of communiols A and B, respectively. Although the ^{1}H and ^{13}C NMR data of each synthetic sample were exactly the same as those of the corresponding natural sample, their specific rotation values showed inexplicable discrepancies. We feel the need for remeasurement of the specific rotation values of natural communiols A and B.

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