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Stereoselective synthesis of *ent*-communiols A–C

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Abstract—The first total synthesis of the non-natural enantiomers of the fungal metabolites communiols A–C is reported. A stereochemical misassignment has been corrected and the absolute configurations of the natural products have been unambiguously established.

The communiols A–H **1**–**8** (Fig. 1) constitute a group of eight polyketide metabolites very recently isolated from a strain of the coprophilous fungus *Podospora communis* (Speg.) Niessl.[1,2] Except for **7**, these molecules are characterized by containing at least one tetrahydrofuran ring in their structures, a feature present in many relevant bioactive metabolites such as lignans[3] and annonaceous acetogenins.[4] Furthermore, communiols E **5** and F **6** display an isolated cyclopenta[*b*]furan system, a not very common feature in natural products from fungal origin. Some of the communiols exhibit antibacterial activity against strains of *Bacillus subtilis* and *Staphylococcus aureus*.[1,2] In the course of our ongoing research program aimed at the stereoselective synthesis of bioactive natural products, we have decided to undertake the stereoselective preparation of these molecules. Our initial targets were communiols A–C, which exhibit the putative structures **1**–**3**.

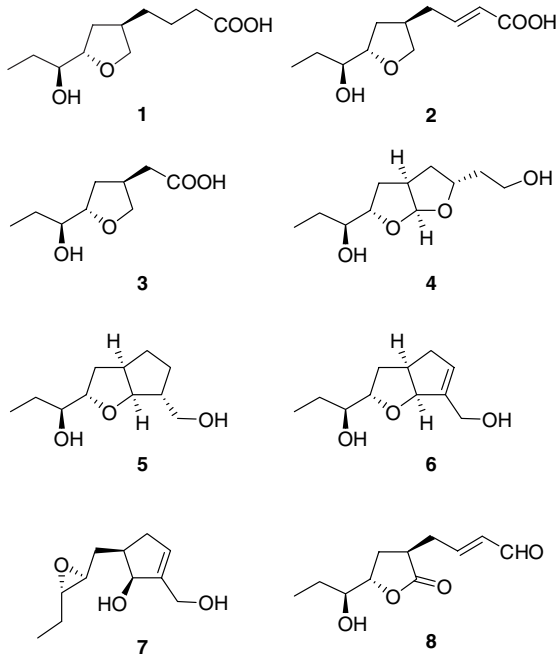

Figure 1. Proposed structures of communiols A–H.

In our design of an efficient and convergent synthetic plan for these metabolites, we envisaged the stereoselective build-up of the tetrahydrofuran ring as the first structural feature to be created. There are a good deal of synthetic methods for the preparation of polysubstituted tetrahydrofuran systems.[5] Our retrosynthetic concept is shown in Scheme 1. Compounds **1**–**3** are retrosynthetically related to tetrahydrofuran **9**, to be obtained by means of a two-step reduction of lactone **10**, prepared in turn through stereoselective allylation of the known compound **11**.[6]

Scheme 2 depicts the details of the synthesis. Lactone **11** has been previously prepared in four steps from L-glutamic acid[6] but we have obtained it in two steps from the known unsaturated ester **12**.[7] Sharpless dihydroxylation[8] of the latter gave the expected γ,δ-dihydroxy ester, which then spontaneously cyclized to **11**. Protection as

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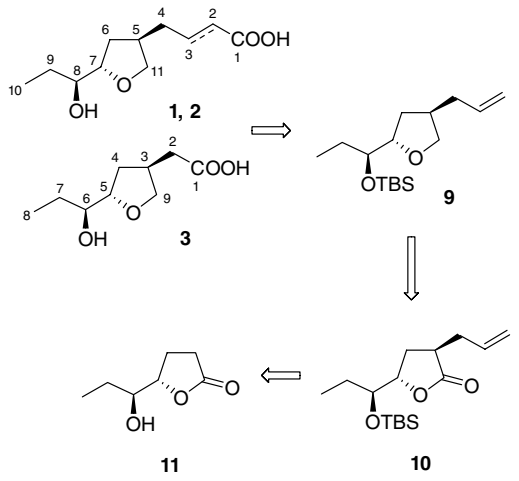
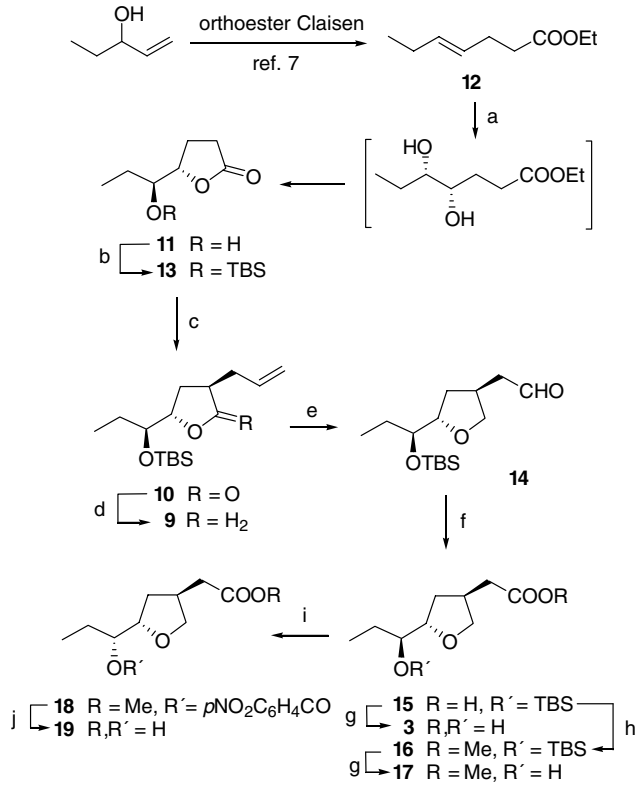


Scheme 1.

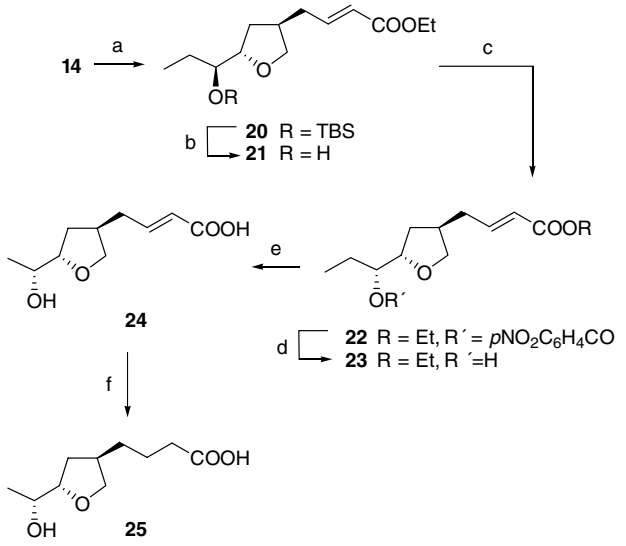


Scheme 2. Reagents and conditions: (a) AD-mix-α, aq *t*-BuOH, 18 h, 0 °C, 84%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 1 h, rt, 93%; (c) LDA, THF, 1 h, −78 °C, then allyl bromide, 1 h, −78 °C, 83% (d.r. 92:8); (d) DIBAL, THF, −78 °C, 15 min, then CF_3COOH, Et_3SiH, CH_2Cl_2, −40 °C, 30 min, 86% overall; (e) OsO_4, NMO, *t*-BuOH, aq THF, 1.5 h, rt, then $NaIO_4$, 1 h, rt, 77% overall; (f) $NaClO_2$, 2-methyl-2-butene, aq *t*-BuOH, NaH_2PO_4, 3 h, rt, 91%; (g) 48% aq HF, MeCN, 1 h, rt, 90%; (h) CH_2N_2, Et_2O, rt, 97%; (i) DIAD, Ph_3P, *p*-$NO_2C_6H_4COOH$, THF, 2 h, rt, 83%; (j) NaOH, MeOH, 2 h, rt, 77%.

the TBS (*t*-butyldimethylsilyl) derivative was followed by α-allylation via the lithium enolate.[9] The reaction took place with a very good stereoselectivity and provided lactone **10** in 83% yield as a separable 92:8 diastereomeric mixture. Reduction of **10** to tetrahydrofuran **9** was performed using a two-step procedure[10] via the intermediate lactol. Oxidative cleavage of the olefinic bond in **9** was performed via an osmylation-periodate sequence[11] and gave aldehyde **14**. The latter was then subjected to oxidation to acid **15** and subsequent deprotection to **3**, which has the structure published for communiol C. Unexpectedly, the physical and spectral properties[12] of the synthetic compound **3** turned out to be different from those reported for communiol C. After a careful revision of the published spectral data, we wondered whether the relative configuration reported for the oxygenated carbon atoms C-5 and C-6 might be wrong. Thus, acid **15** was methylated and desilylated to ester **17**, which was then subjected to hydroxyl inversion by means of the Mitsunobu reaction.[13] This yielded ester **18**, saponification of which provided acid **19**. The latter proved identical with communiol C in all its spectral properties (the question of the optical rotation will be addressed below, together with the other communiols).

It thus appeared that the stereostructure of communiol C had not been correctly assigned as regards the hydroxyl-bearing side chain. In view of this fact, we assumed that the same configurational misassignment was also present in all other members of the series. Accordingly, our initial synthetic plan was modified. Scheme 3 shows the reactions, which led eventually to the preparation of communiols A and B.

Aldehyde **14** was subjected to a Horner–Wadsworth–Emmons olefination under mild conditions.[14] This provided conjugated ester **20**, which was then desilylated to alcohol **21**. Mitsunobu inversion of the secondary hydroxyl group in the latter afforded **22**. Sequential saponification[15] of the two ester residues gave hydroxy acid **24**, which exhibited spectral properties distinctly matching those published for communiol B.[1] Finally,



Scheme 3. Reagents and conditions: (a) $(EtO)_2P(O)CH_2COOEt$, LiCl, DIPEA, MeCN, 12 h, rt, 81%; (b) 48% aq HF, MeCN, 1 h, rt, 88%; (c) DEAD, Ph_3P, *p*-$NO_2C_6H_4COOH$, THF, 2 h, rt, 78%; (d) LiOH, aq THF, 2 h, rt, 91%; (e) NaOH, aq THF, 5 h, Δ, 85%; (f) H_2, Pd/C, EtOAc, 2 h, 96%.

hydrogenation of the olefinic bond in **24** furnished hydroxy acid **25**, with spectral properties identical to those published for communiol A.[1]

With the relative stereostructures of communiols A–C now unambiguously assigned, we went on to establish their absolute configurations. The question, however, proved to be somewhat less clear-cut than expected. Communiols A–C, most particularly communiol B, were isolated in very small amounts, thus the reported optical rotation values[16] are likely affected by non-negligible errors. To complicate matters still more, we have found that both absolute value and sign of the optical rotations of synthetic **19**, **24** and **25** are markedly dependent on the concentration. For instance, the following values have been observed: **19**, $[\alpha]_D$ −13.4 (*c* 0.30, CH_2Cl_2); $[\alpha]_D$ −58.9 (*c* 0.13, CH_2Cl_2); **24**, $[\alpha]_D$ −2.1 (*c* 0.7, CH_2Cl_2); $[\alpha]_D$ +18.6 (*c* 0.14, CH_2Cl_2); $[\alpha]_D$ +64.3 (*c* 0.07, CH_2Cl_2); **25**, $[\alpha]_D$ +0.5 (*c* 2.2, CH_2Cl_2); $[\alpha]_D$ +7.1 (*c* 0.55, CH_2Cl_2); $[\alpha]_D$ +18.8 (*c* 0.22, CH_2Cl_2); $[\alpha]_D$ +91.8 (*c* 0.05, CH_2Cl_2). Such changes in value and sign are well precedented in chiral carboxylic acids, and have been attributed to association phenomena.[17]

At concentration values similar to those used in the original publication,[1] the optical rotations of synthetic hydroxy acids **24** and **25** are opposite in sign to those of the natural compounds, even if the absolute numerical values are appreciably different. Assuming that the reported optical rotation values and signs of natural communiols A and B[1,16] are reliable at such dilute concentrations, we may conclude that synthetic compounds **24** and **25** are the enantiomers of these naturally occurring metabolites (Fig. 2). The case of communiol C is special, as the negative sign of the optical rotation is the same in both the natural and the synthetic compound. However, the NMR spectra of the natural sample, kindly sent by Professor Gloer, shows visible amounts of an impurity, which is, in all likelihood, communiol B. Since the negative optical rotation of the latter is much higher in its absolute value than that of communiol C (assumedly positive), it is likely that this impurity has affected the measured value of the optical rotation of communiol C, even to the point of changing the sign. Since it is not logical from the biosynthetic point of view that communiol C belongs to a different stereochemical series than the other members of the group, we may safely conclude that the latter compound has the absolute configuration depicted in Figure 2.

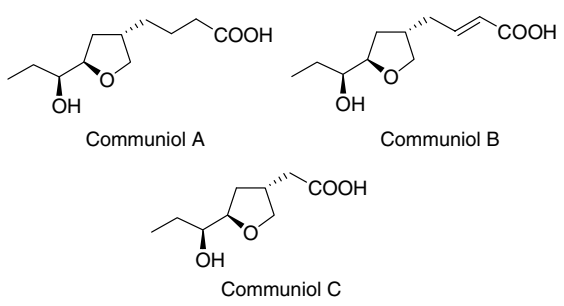


Figure 2. Absolute stereostructures of communiols A–C.

In summary, we have performed the first stereoselective synthesis of the non-natural enantiomers of the fungal metabolites communiols A–C. Furthermore, we have corrected a misassignment in the reported relative stereostructures and determined the absolute configurations of the natural compounds. A more detailed account of the preparation of these and other communiols will be reported in the near future.

Note added in proof

After our manuscript was sent to the journal, a synthesis of communiols A–C was published alongside a reaction sequence essentially identical to ours (see Ref. 18).

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.115.

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11. Ozonolysis of **9** gave low yields in **14**, due to competitive attack to the methylene contiguous to the oxygen atom.
12. Compound **3**: oil, $[\alpha]_D$ −4.8 (*c* 1.4; CH_2Cl_2). IR ν_{max} 3400–2400 (br, acid OH), 1714 (acid C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.06 (1H, dd, $J = 8.6$, 6.6 Hz, H-9_a), 3.87 (1H, q, $J = 7$ Hz, H-5), 3.48 (1H, dd, $J = 8.6$, 6.2 Hz, H-9_b), 3.35 (1H, m, H-6), 2.68 (1H, m, H-3), 2.44 (2H, d, $J = 7.5$ Hz, H-2_a/2_b), 1.94 (1H, dt, $J = 12.5$, 7 Hz, H-4_a), 1.70 (1H, ddd, $J = 12.5$, 7.4, 5.7 Hz, H-4_b), 1.55-1.40 (2H, br m, H-7_a/7_b), 0.99 (3H, t, $J = 7.5$ Hz, H-8); ^{13}C NMR (125 MHz) δ 177.0 (C), 81.4, 75.2, 35.6 (CH), 72.9, 37.3, 34.0, 26.5 (CH_2), 10.1 (CH_3).
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15. Attempts at one-pot saponification of both ester residues with NaOH/MeOH gave low yields in **24**, due in part to problems in the separation of **24** from the accompanying *p*-nitrobenzoic acid.
16. Reported values for natural communiols[1] are: communiol A, $[\alpha]_D$ −1.6 (*c* 0.25, CH_2Cl_2); communiol B, $[\alpha]_D$ −95 (*c* 0.075, CH_2Cl_2); communiol C, $[\alpha]_D$ −3.4 (*c* 0.142, CH_2Cl_2).
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