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Total syntheses of (+)-adunctins C and D: assignment of their absolute configurations†

Jian Xiao,[a] Jun Zhao,[a] Ya-Wen Wang,[a] Gan Luo[b] and Yu Peng *[a]

The first total synthesis of (+)-adunctin C (*ent*-1) and (+)-adunctin D (2), two monoterpene-substitued dihydrochalcones isolated from *Piper aduncum* (Piperaceae), was achieved. A regioselective oxidative [3 + 2] cycloaddition of acylphloroglucinol with (−)-β-phellandrene was developed to construct their unique spirobenzofuran skeleton. The absolute configurations of natural adunctins 1 and 2 were thus assigned through these endeavors.

Piper aduncum L., a monoecious shrub or slender tree, is the largest genus in the economically and medicinally important Piperaceae family. It has been used as a traditional medicine in Malaysia and in a large part of tropical America. In particular, in Papua New Guinea, Peru and Colombia, its leaves are used for the treatment of fresh wounds and diarrhoea,[1] and against dysentery and as a haemostatic.[2] Adunctins C (**1**) and D (**2**)[3] were isolated from the leaves of *Piper aduncum* by Sticher and co-workers in 1993 (Fig. 1). These two molecules showed antibacterial effects against *Micrococcus luteus* at concentrations of 2.4 μg mL^{-1} and 2.9 μg mL^{-1}, respectively. Structurally, adunctins C (**1**) and D (**2**) feature a spirobenzofuran skeleton and two stereogenic centers, including a spirocyclic quaternary carbon. Their relative configurations at C(1) and C(4) have been established by 1D and 2D-NMR spectroscopy; however, the corresponding absolute configurations are still unknown. Notably, these tricyclic spirobenzofuran derivatives have received considerable attention due to their biological and pharmaceutical activities.[4] In particular, griseofulvin (**3**) is known as an antifungal agent and exhibits good anticancer and antiviral properties.[5] Thus, several synthetic routes have been established for its preparation.[6] Surprisingly, no related synthesis of adunctins C (**1**) and D (**2**) has been reported until now. Furthermore, their absolute configurations at C(1) and C(4) are still not established. In connection with our previous synthesis of divergent natural products,[7] herein, we report the first asymmetric syntheses of adunctins C and D and the assignment of their absolute stereochemistries.

We designed a formal [3 + 2] cycloaddition for assembling the spirobenzofuran core of these two molecules (Scheme 1). Under oxidation conditions, dihydrochalcone (**4**) generates the radical intermediate **I**, which undergoes a regioselective radical addition with β-phellandrene (**5**) to give the tertiary radical **II**. This step is enantiodivergent due to the availability of either of the two enantiomers of **5**. Further oxidation of these species formed cation **III**, which was intramolecularly trapped by the carbonyl or the hydroxyl group from the rearomatization, leading to the construction of the key spirobenzofuran and thereby completing the total synthesis of natural adunctins C and D or their antipodes. The concise route shown in Scheme 1 not only provides a flexible approach for the determination of the absolute stereochemistries of these

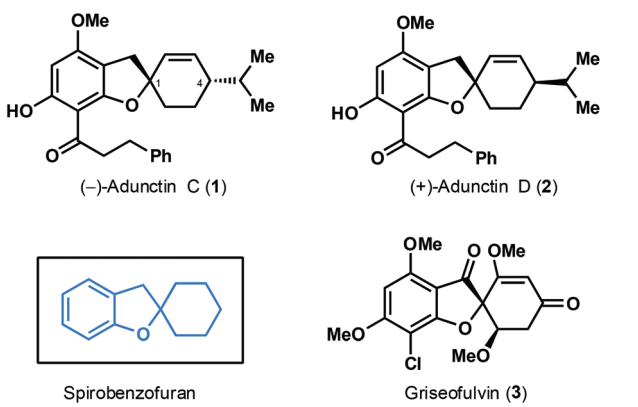

Fig. 1 Representative natural products containing the spirobenzofuran framework.

[a]*Sichuan Engineering Research Center for Biomimetic Synthesis of Natural Drugs, School of Life Science and Engineering, Southwest Jiaotong University, Chengdu 610031, People's Republic of China. E-mail: pengyu@swjtu.edu.cn*
[b]*West China School of Pharmacy, Sichuan University, Chengdu 610041, People's Republic of China*

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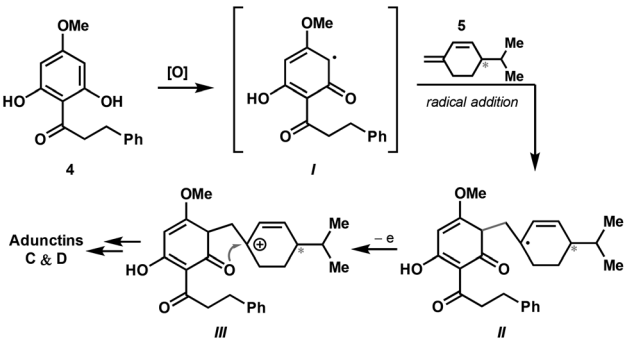


Scheme 1 Enantiodivergent approach for the formation of adunctins C and D.

two monoterpene-substituted dihydrochalcones, but also sheds light on the plausible biosynthetic pathway[8] for obtaining these types of spirobenzofuran natural products.

As shown in Scheme 2 (left), (−)-β-phellandrene (**5**) was prepared from commercially available 4-isopropylcyclohexanone **6**. Its conversion into chiral cyclohexenone **9** was carried out based on a reported procedure,[9] with our modifications. The enantioselective deprotonation of **6** with chiral lithium amide (*R*)-**7** followed by the quenching of the *in situ* generated enolate with TMSCl gave silyl enol ether **8**, which was then subjected to the Saegusa oxidation system using $Pd(OAc)_2/O_2$, and (*R*)-cryptone **9** was afforded in 89% yield and with 87%ee. Its absolute configuration was determined by a comparison of its optical rotation with that in previous report (see the ESI†). The subsequent Wittig reaction gave (−)-**5** in 83% yield.[10] Notably, the facile synthesis of *rac*-**5** was achieved by an analogous protocol *via* the intermediacy of *rac*-**8** (see the ESI† for details). Meanwhile, another building block (**4**) was easily synthesized as well (Scheme 2, right). The selective methylation of phloroglucinol **10** using Me_2SO_4 and K_2CO_3 afforded its monomethyl derivative, which then underwent Friedel–Crafts acylation with the freshly made phenylpropanoyl chloride and eventually afforded dihydrochalcone **4** in 42% yield.[11]

With dihydrochalcone **4** and β-phellandrene **5** (*rac* or levorotatory) in hand, the designed oxidative [3 + 2] cycloaddition[12] was then performed. First, a mixture of **4** and (±)-**5** was treated with Ag_2O in acetonitrile at 55 °C; as expected, the reaction proceeded well to give racemic adunctin C and adunctin D, although they could not be separated by flash column chromatography. However upon recrystallization from hexane, yellow prism crystals were formed. After filtration, pure *rac*-**1** was obtained in 47% yield, and further evaporation of the filtrate afforded the colorless *rac*-**2** in 22% yield. Fortunately, single crystals of both products were obtained by slow evaporation of solvents at room temperature. X-ray diffraction analysis of single crystals[13] unambiguously disclosed their structures (Fig. 2, selected H atoms have been omitted for clarity; Tables S1 and S2†), thereby confirming the respective relative configurations proposed by Sticher and co-workers.[3]

Next, the asymmetric synthesis of these two molecules under the same oxidation conditions was carried out starting from chiral β-phellandrene (−)-**5** (Scheme 3). Not surprisingly, the corresponding optically pure products were successfully obtained with equal efficiency. Their ^{1}H NMR and ^{13}C NMR data (Tables S4 and S5†) were consistent with those of the natural adunctins C and D provided in the literature.[3] Meanwhile, natural adunctin D (**2**) shows an optical rotation of +31.0 (*c* = 0.52, MeOH), and our synthetic sample showed a rotation of +32.45 (*c* = 0.84, MeOH). Altogether, it is concluded

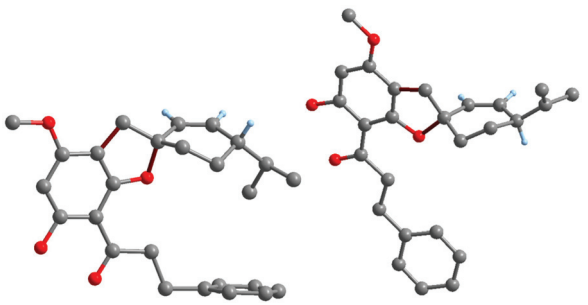
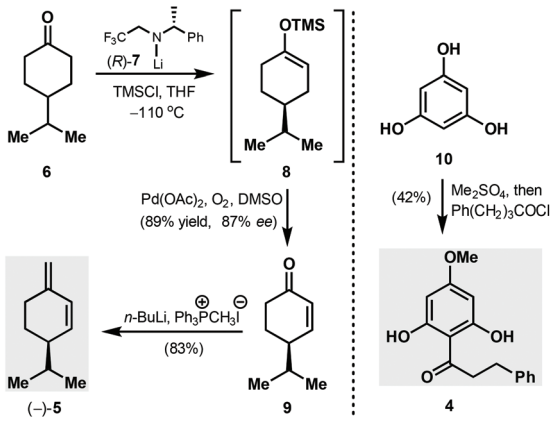
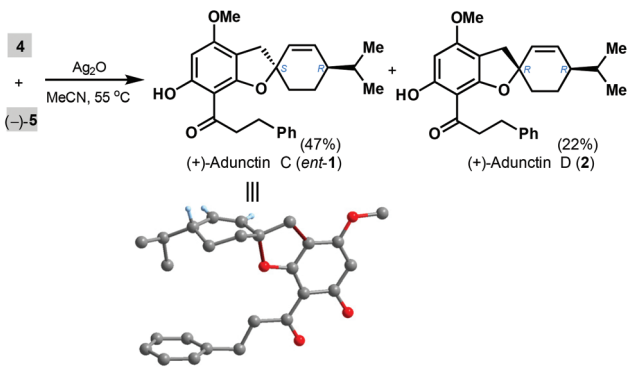


Fig. 2 X-ray crystal structures of racemic adunctin C (left) and adunctin D (right).



Scheme 2 Preparation of (−)-β-phellandrene **5** and dihydrochalcone **4**.



Scheme 3 Unified syntheses of (+)-adunctin C (*ent*-**1**) and (+)-adunctin D (**2**).

that the first synthesis of natural adunctin D (**2**) has been achieved, and its absolute configurations is assigned as (1*R*,4*R*). As for adunctin C, natural adunctin **1** shows an optical rotation of −71.4 (*c* = 0.73, MeOH), while our synthetic sample shows a rotation of +122.1 (*c* = 0.47, MeOH), and its structure was further confirmed by single-crystal X-ray analysis with Cu-Kα radiation (see the inset in Scheme 3 and Table S3†).[13] We actually obtained an antipode [(1*S*,4*R*)-*ent*-**1**] of the natural (−)-adunctin C, whose absolute configurations is assigned as (1*R*,4*S*). Natural adunctin C (**1**) could thus be potentially synthesized from **4** and (+)-**5**, which could be prepared from (*S*)-**7** (from commercially available (*S*)-1-phenylethylamine)[14] *via* a similar pathway, as shown in Scheme 2.

In summary, (+)-adunctins C and D have been synthesized *via* an oxidative [3 + 2] cycloaddition[15] with excellent regioselectivity. This key annulation reaction is a versatile method to construct an embedded spirobenzofuran skeleton. It is envisioned that bioactive natural products with related structures can be accessed using the present biomimetic strategy.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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