Natural Product Synthesis

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Total Synthesis of (+)-Lactiflorin by an Intramolecular [2+2] Photocycloaddition**

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The final confirmation of a structure assignment has remained one of the preeminent tasks of natural product synthesis. Despite the advancement in analytical techniques, there are several cases in which the synthesis of a compound with the proposed structure of a natural product has led to a correction of the original assignment.[1,2] Along these lines, we were intrigued by (+)-lactiflorin, a natural product first isolated from the roots of *Paeonia lactiflora* Pall.[3] The same compound was also isolated from the related species *Paeonia anomala var. intermedia* (C. A. Mey.) O. & B. Fedtsch.[4] Three structures **1**–**3** have been suggested for (+)-lactiflorin.[3–5] The numbering of compounds **2** and **3** in Figure 1 has been taken from the original papers. A total synthesis of (+)-lactiflorin has not yet been achieved.

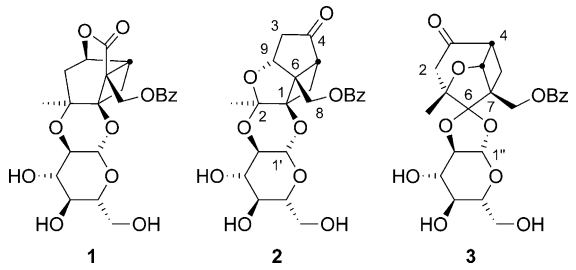

Figure 1. Previously proposed structures **1**–**3** of (+)-lactiflorin.

Although the fact that natural (+)-lactiflorin can be converted in low yield into paeoniflorin (**4**)[6,7] and although a biogenetic congener compound, which can be tentatively described by structure **5** (Figure 2), makes structure **2** the most likely structure for (+)-lactiflorin, it was desirable to provide synthetic evidence for this assumption. We therefore embarked on a total synthesis of compound **2** with the aim to use a [2+2] photocycloaddition reaction[8] as one of the key steps in the reaction sequence.[9,10] In this manuscript we present preliminary results of this research, which culminated in the total synthesis of (+)-lactiflorin and its unambiguous structure proof.

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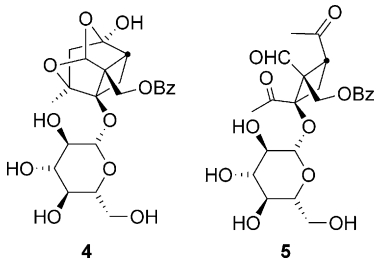
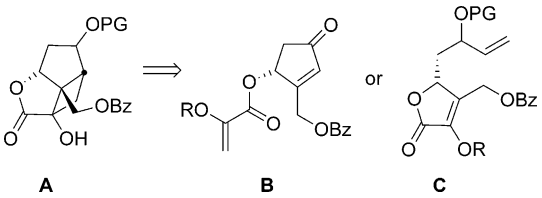


Figure 2. Structures of (−)-paeoniflorin (**4**) and of a putative common intermediate **5** of compounds **2** and **4**.

It was envisioned that a retrosynthetic disconnection at the glycosidic bond would lead to a subunit of compound **2**, which could be derived from D-glucose, and to a tricyclic aglycon with general structure **A** (Scheme 1), which could be



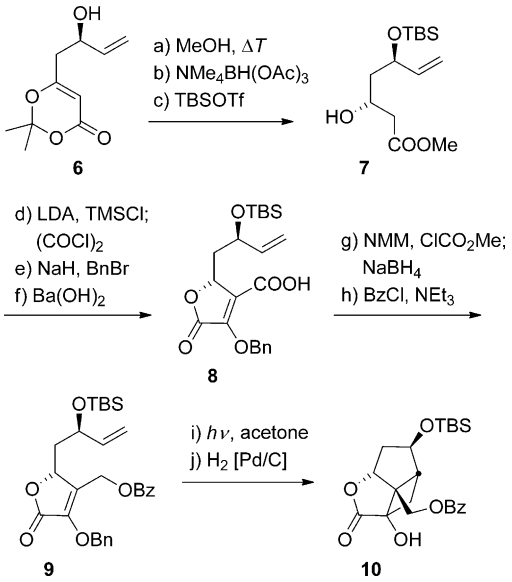
Scheme 1. Possible ways of obtaining tertiary alcohol **A** by intramolecular [2+2] photocycloaddition of precursors **B** or **C**.

accessible by intramolecular [2+2] photocycloaddition reactions.[8] Conceivable precursors were the β,γ-substituted cyclopentenone **B** and the α,β,γ-trisubstituted α,β-unsaturated lactone **C**. Preliminary studies with model compounds revealed that the intramolecular [2+2] photocycloaddition of substrates **B** was not feasible. When we employed readily available, pyruvate-derived silyl enol ethers (R = trimethylsilyl), which had been shown in intermolecular [2+2] photocycloaddition reactions to be competent alkene substrates,[11] we were not able to detect the desired products upon irradiation at $\lambda = 300$ nm or $\lambda = 350$ nm in various solvents.

With model compounds related to lactone **C**, the initial screening was more successful. Clean photocycloaddition products were obtained, the constitution (*straight* or *crossed*) of which turned out to be dependent on the relative configuration of the protected (PG = protecting group) secondary alcohol. Since the corresponding alcohol will eventually be oxidized to a ketone (C4 in structure **2**), this stereogenic center, which is in a 1,3-diol relationship to the stereogenic center at the lactone, can be freely chosen. Based on preliminary studies an *anti*-1,3-diol configuration[12] deliv-

ered the best results in the intramolecular [2+2] photocycloaddition reaction.

The synthesis of a suitable [2+2] photocycloaddition precursor commenced with enantiomerically pure (2′*R*)-2,2-dimethyl-6-(2′-hydroxybut-3′-enyl)-1,3-dioxin-4-one (**6**)[13] (Scheme 2). Refluxing of dioxinone **6** and methanol in

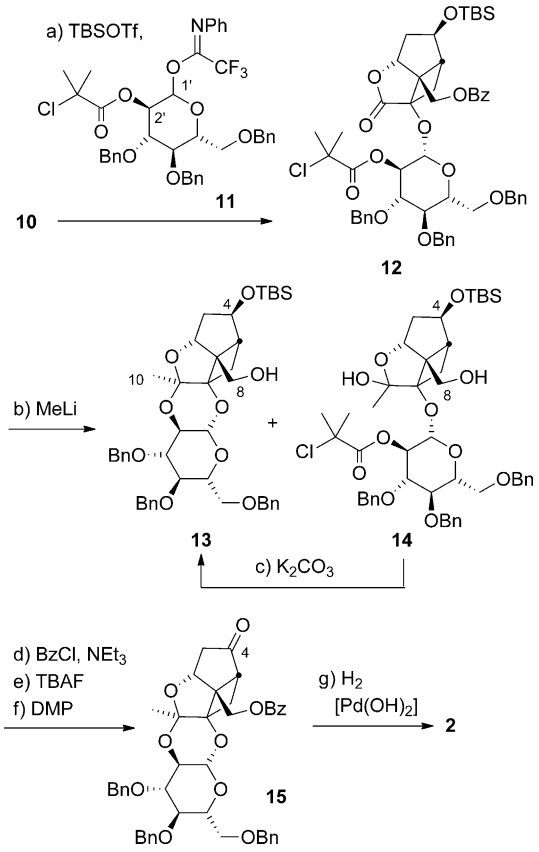


Scheme 2. Synthesis of aglycon **10**; exact conditions and yields: a) Methanol (2.8 equiv), toluene, reflux, 3 h, 78%; b) $NMe_4BH(OAc)_3$ (5 equiv), CH_3CN/HOAc, −35 °C, 44 h, 88%; c) TBSOTf (1.05 equiv), 2,6-lutidine (3 equiv), CH_2Cl_2, −78 °C, 4 h, 90%; d) LDA (2.2 equiv), TMSCl (2.5 equiv), THF, −78 °C→RT, 19 h; then $(COCl)_2$ (1 equiv), CH_2Cl_2, −78 °C→RT, 21 h, 61%; e) NaH (2 equiv), BnBr (2 equiv), DMF, RT, 21 h, 67%; f) $Ba(OH)_2{\cdot}8H_2O$ (5 equiv), THF/H_2O, 60 h, 71%; g) NMM (1 equiv), $ClCO_2Me$ (1 equiv), THF, −10 °C, 0.5 h; then $NaBH_4$ (3 equiv), MeOH, 0 °C, 0.5 h, 63%; h) BzCl (1.5 equiv), DMAP (0.2 equiv), NEt_3 (2 equiv), CH_2Cl_2, 0 °C→RT, 1 h, 91%; i) *hν* ($\lambda = 300$ nm), CH_3CN/acetone, RT, 2 h; (j) H_2, Pd/C (0.5 equiv), EtOH, RT, 16 h, 53% over 2 steps. Bn = benzyl, Bz = benzoyl, DMAP = 4-dimethylaminopyridine, NMM = *N*-methylmorpholine, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate.

toluene, *anti* reduction[14] of the resulting β-keto ester, and selective TBS protection[15] of the 1,3-diol led to β-hydroxy ester **7**. Cyclization of a 1,3-bis(silyloxy)alk-1-ene, which was generated from **7** in situ, with oxalyl chloride[16] allowed for the formation of the butenolide chromophore. Subsequent *O*-benzylation and selective saponification provided compound **8**. Two-step reduction of the carboxylic acid[17] and benzoylation of the resulting primary alcohol furnished the [2+2] photocycloaddition precursor **9**.

Irradiation of substrate **9** at $\lambda = 300$ nm gave the intramolecular photocycloaddition products with similar regioselectivity (*straight*/*crossed* ≅ 75:25)[18] irrespective of the other reaction conditions (i.e. variation of solvent, glassware, reaction time). The reaction went to full conversion in two hours when acetone ($E_T = 332$ kJ mol^{-1})[19] was chosen as a sensitizing co-solvent (Duran filter). Since the regioisomers were not separable at this stage, the hydrogenolysis of the intermediate benzyl ether was performed with the mixture of regioisomers. Chromatographic separation delivered aglycon **10** as a single diastereomer in 53% yield over two steps starting from substrate **9**. The relative configuration of compound **10** was confirmed by extensive two-dimensional NMR experiments.

Glucosyl acceptor **10** turned out to be unstable under basic conditions. Glucosylation attempts were therefore limited to reactions in which the glycosidic linkage was formed under neutral or acidic conditions. Various leaving groups (at C1′) and neighboring groups (at C2′) were tested[20] on the tribenzylated glucosyl donor derived from D-glucose.[21] The best results have so far been obtained with glucosyl donor **11**, which bears *N*-phenyltrifluoroacetimidate (PTFAI)[22] as the leaving group at C1′ and the 2-chloro-2-methylpropanoyl group[23] as the protecting group for the alcohol at C2′ (Scheme 3). The fact that the glucosyl acceptor is a tertiary alcohol renders the glycoside formation difficult and may also be responsible for the limited diastereoselectivity.[24] Despite the expected neighboring-group participa-



Scheme 3. Completion of the synthesis of (+)-lactiflorin (**2**); exact conditions and yields: a) **11** (3 equiv), TBSOTf (0.4 equiv), 4 Å MS, hexane/CH_2Cl_2, 0 °C, 12 h, 26% for **12**, and 44% for α anomer; b) MeLi (13 equiv), THF, −78 °C, 5 h; then PPTS, CH_2Cl_2, RT, 3 h, 70%; c) K_2CO_3 (3 equiv), MeOH/THF, then PPTS, CH_2Cl_2, RT, 3 h, quant.; d) NEt_3 (5 equiv), DMAP (1 equiv), BzCl (5 equiv), CH_2Cl_2, 18 h, 88%; e) TBAF (3.4 equiv), THF, RT, 2 h; f) DMP (3 equiv), $NaHCO_3$ (8 equiv), CH_2Cl_2, RT, 4 h, 81% over 2 steps; g) $Pd(OH)_2$/C, H_2, EtOH, RT, 4 h, 99%. TBAF = tetra-*n*-butylammonium fluoride, DMP = Dess–Martin periodinane, PPTS = pyridinium *para*-toluenesulfonate.

tion of the 2-chloro-2-methylpropanoyl group, the desired β-glycoside **12** was isolated in only 26% yield, along with the readily separable α anomer as the other product (44% yield).

The missing methyl group was introduced by methyl addition to glycoside **12**. It turned out that the reaction was—under a variety of conditions—not selective towards reaction at the lactone unit. Consequently, an excess of methyllithium was employed, delivering a ketone intermediate, which could be cyclized to ketal **13** under acidic conditions. In some cases the C2′-protected alcohol **14** was obtained as a side product in the methyl-addition step. Separation from the ketone was feasible and after deprotection, the latter compound was quantitatively converted into the former. As expected, the primary hydroxy group (at C8) did not participate in ketal formation because of the geometric constraints exerted by the rigid cyclobutane ring. Benzoylation of primary alcohol **13**, cleavage of the TBS ether at C4, and oxidation with Dess–Martin periodinane (DMP) smoothly furnished the triply benzylated intermediate **15**. Global debenzylation with Pearlman's catalyst gave compound **2**, the ^{13}C NMR spectrum of which perfectly matched the reported spectrum of lactiflorin[4] (see the Supporting Information). The specific rotation was also in agreement with the reported value.

However, there was some ambiguity regarding the ^{1}H NMR data provided by Iskander et al.[4] Most significantly, for a spectrum recorded at a field strength of 300 MHz they reported a doublet of triplets at $\delta = 2.79$ ppm with coupling constants of $J = 13.2$, 4.5, 4.5 Hz (assigned to H4 in structure **3**) and at $\delta = 2.80$ ppm a doublet with $J = 18.0$ Hz (assigned to H2β), while our data at a field strength of 500 MHz suggested two doublets of doublets with $J = 17.5$, 4.6 Hz at $\delta = 2.80$ ppm and $J = 13.0$ Hz, 4.9 Hz at $\delta = 2.81$ ppm. Further clarification was expected from lactiflorin triacetate (**16**, Figure 3), the synthesis of which was readily achieved upon treatment of triol **2** with acetic anhydride in pyridine (59% yield).

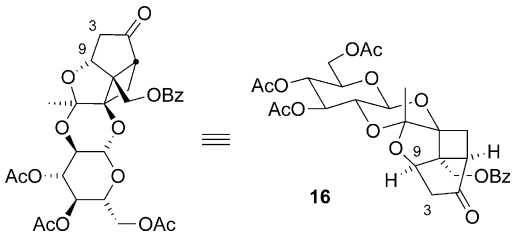


Figure 3. Structure of lactiflorin triacetate (**16**) as obtained from **2** by treatment with Ac_2O (pyridine).

The ^{13}C NMR data (in $CDCl_3$) and the ^{1}H NMR data (in $CDCl_3$ and C_6D_6) of this compound matched the data previously reported in all respects.[4,5] The NMR data also reveal the reason for the wrongly assigned structure **3** for lactiflorin. As mentioned above, Iskander et al. had assigned only two doublets to the protons at C2 of their putative structure **3**: "*These protons did not show further coupling and were presumed to be connected to two quaternary carbons*".[4] This interpretation turned out to be incorrect, because one of these protons (at C3 in structures **2** and **16**) does show a further coupling, that is, a vicinal coupling ($J = 4.6$ Hz) to the proton at C9. The other suggested structure **1** of lactiflorin had been previously corrected because of a wrong interpretation of the ketone carbonyl signal.[5]

In conclusion, we have achieved the first total synthesis of (+)-lactiflorin (**2**) starting from the known dioxinone **6** in 16 steps (0.7% overall yield). The synthesis proves unambiguously one of the previously suggested structures (structure **2**, Figure 1) of this natural product. Further studies regarding a potential common synthetic precursor to lactiflorin and paeoniflorin continue in our laboratory.

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