Natural Product Synthesis

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Total Synthesis of (+)-Clavolonine, (−)-Deacetylfawcettiine, and (+)-Acetylfawcettiine**

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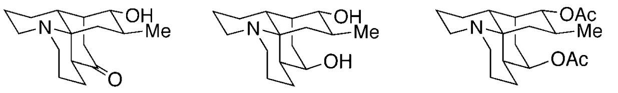
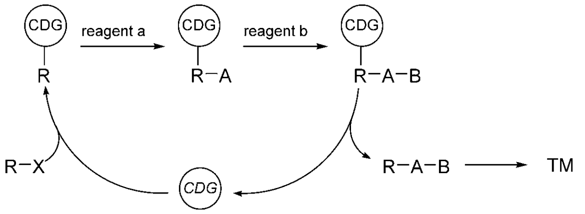
Lycopodium alkaloids have attracted great interest from a biological and biogenetic point of view during the past decades.[1] Over 200 alkaloids with structurally diverse skeletons have been isolated so far.[2a] The complex structures make them challenging targets for total synthesis and a playground for the exploration of new methodology. (+)-Clavolonine (**1**), (−)-deacetylfawcettiine (**2**), and (+)-acetylfawcettiine (**3**) are members of the genus Lycopodium alkaloid (family *Lycopodiaceae*) and contain the unique heterocyclic C_{16}N-Lycopodium skeleton (Scheme 1).[2b] (+)-Clavolonine was first isolated in 1960 from the club moss *Lycopodium clavatum*,[3] and (−)-deacetylfawcettiine[4a] in 1959 as well as (+)-acetylfawcettiine[4b] one year later both from *Lycopodium fawcettii*. These types of alkaloids are widely used in traditional Chinese medicine and homeopathic therapies.[5] Until today only the racemic synthesis[6] for (−)-deacetylfawcettiine (**2**) and (+)-acetylfawcettiine (**3**), and one enantioselective total synthesis[7] of (+)-clavolonine (**1**) are known.



(+)-clavolonine (**1**) (−)-deacetylfawcettiine (**2**) (+)-acetylfawcettiine (**3**)

Scheme 1. C_{16}N-Lycopodium alkaloids.

Recently, our research group has reported a new strategy for stereoselective organic synthesis relying on substrate control (Scheme 2).[8] Thus, with the aid of one directing group a sequence of stereoselective, catalytic carbon skeleton extensions is achieved, before the directing group is removed from the substrate. Herein we report a new implementation of this strategy through stereoselective total synthesis of the three C_{16}N-Lycopodium alkaloids: (+)-clavolonine (**1**), (−)-deacetylfawcettiine (**2**), and (+)-acetylfawcettiine (**3**).



Scheme 2. Concept of CDG-controlled organic synthesis CDG = catalyst-directing group, TM = target molecule.

Retrosynthetically, both (−)-deacetylfawcettiine (**2**) and (+)-acetylfawcettiine (**3**) could be derived from (+)-clavolonine (**1**) through postmodifications of functional groups.[9] Hence, our retrosynthesis focused on the skeleton of (+)-clavolonine (**1**; Scheme 3). For this strategy we envisioned the late-stage formation of tertiary amine **1** by a Staudinger/Aza-Wittig[10] sequence of azide **6** and subsequent Mannich cyclization and N-alkylation.[11] Azide **6** in turn could be derived from a side-chain elongation of aldehyde **7**. Thus starting from alkene **9**, the stereoselective construction of the central cyclohexane core (shown in bold) of **7** (and **1**) involves two rhodium-catalyzed hydroformylations directed by *ortho*-diphenylphosphanyl benzoyl (*o*-DPPB) and a carbonyl-ene reaction; these reactions have recently been developed by our research group.[12] The absolute configuration of the secondary alcohol function in **9** was to be controlled by way of an asymmetric catalytic reduction of ynone **10**. Hence, all of the remaining five (for **1**, or six for **2** and **3**) stereogenic centers of the target alkaloids should originate from substrate control exclusively.

Our synthesis commenced with the enantioselective construction of bis(alkenyl)carbinol **15** (Scheme 4). Thus, starting from 4-chlorobutanol (**11**) Swern oxidation[13] and subsequent Wittig olefination[14] furnished enoate **12**. Transformation of the ester function into an acid chloride allowed for a Lewis acid mediated acylation of bis(trimethylsilyl)acetylene[15] and gave the enone **10** in 93 % yield over three steps. For installation of the correct carbinol configuration we selected a Corey–Bakshi–Shibata (CBS) reduction protocol.[16] Thus, after cleavage of the TMS group the propargylic alcohol **14** was obtained in 86 % yield (2 steps) with an *ee* value of 98.4 %.[17] Transformation of the terminal alkyne into the required 2-propenyl function required a chemo- and regioselective carbometalation of the alkyne function. This transformation was achieved upon treatment with a methyl-Grignard-derived Normant-type cuprate in good yield

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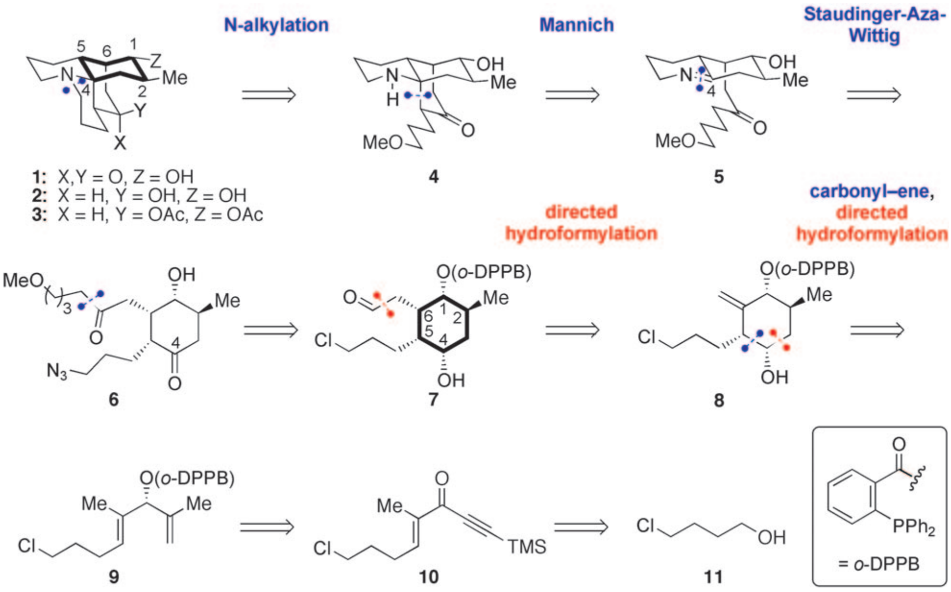
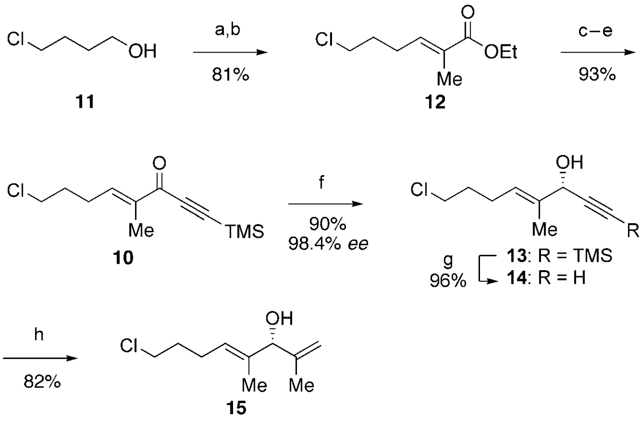


Scheme 3. Retrosynthetic plan. TMS = trimethylsilyl.

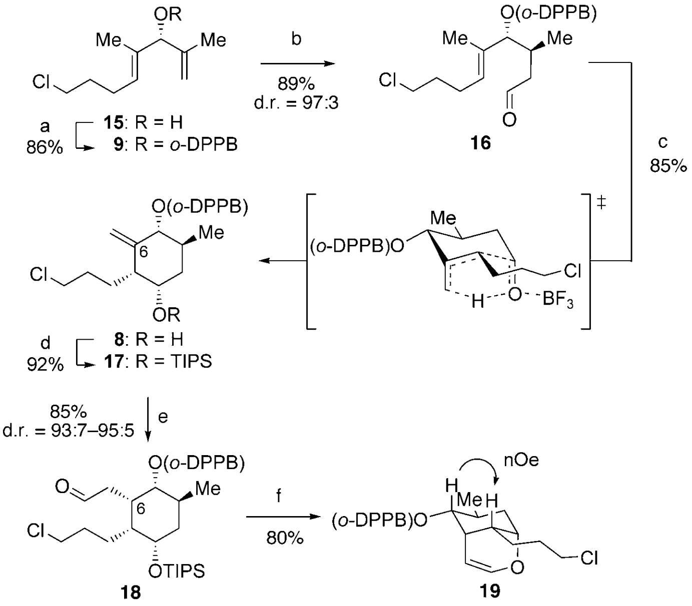


Scheme 4. Synthesis of the unsymmetric carbinol **15**. Reagents and conditions: a) 1) $(COCl)_2$, DMSO, CH_2Cl_2, 2) NEt_3, −78 °C to RT; b) $PH_3PCMeCO_2Et$, toluene, RT, 81 % yield over 2 steps; c) KOH, H_2O, quant.; d) $(COCl)_2$, THF; e) $AlCl_3$, BTMSA, 93 % over three steps; f) (*S*)-Me-CBS, $BH_3{\cdot}SMe_2$, THF, 0 °C, 90 %; g) TBAF, THF, 0 °C to RT, 96 %; h) CuI, MeMgCl, THF, −20 °C, 82 %. BTMSA = bis(trimethylsilyl)-acetylene, TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran.

(82 %).[18] Other known carbometalation protocols were less efficient in our hands.[19]

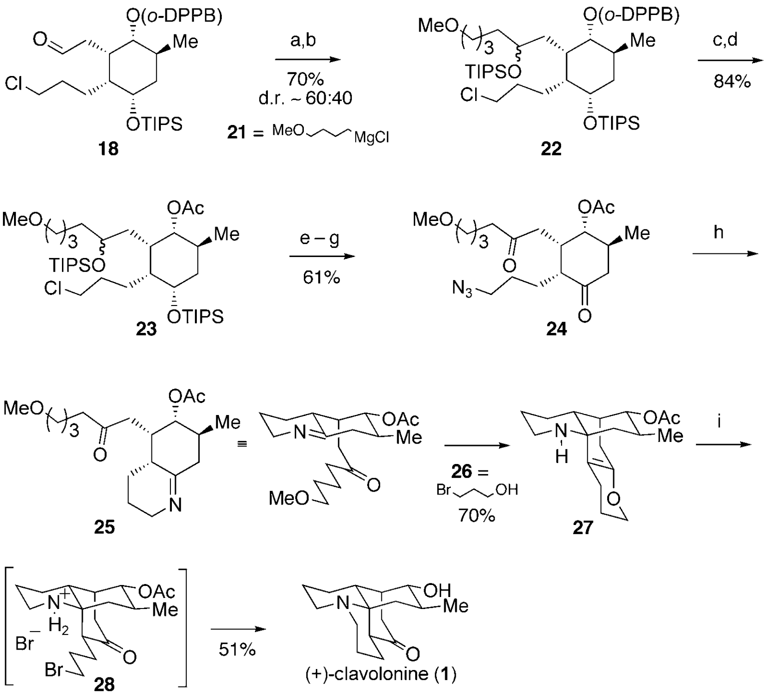
Next the catalyst-directing *o*-DPPB group was installed by employing the Steglich protocol for esterification (Scheme 5).[20] Subjection of *o*-DPPB ester **9** to the conditions of a directed hydroformylation allowed for a smooth chemo-, regio-, and diastereoselective hydroformylation of the 1,1-disubstituted alkene function in the presence of a trisubstituted alkene and furnished *syn*-aldehyde **16** in excellent yield and diastereoselectivity (d.r. = 97:3).[21] Addition of the Lewis acid borontrifluoride and heating to 70 °C in toluene initiated a clean and diastereoselective carbonyl-ene cyclization and gave the highly functionalized cyclohexanol **8**.[12] Alternatively, these two steps could be carried out as a one-pot procedure with comparable yield.[22]

Attempts to achieve a diastereoselective hydroformylation on **8** did not provide sufficient levels of diastereoselectivities (d.r. = 71:29), presumably owing to the fact that the two competing transition states for hydrometalation of the diastereotopic alkene faces are not sufficiently discriminated between in terms of their energy. To set the correct configuration we envisioned blocking the bottom alkene face *syn* to the hydroxy substituent by transformation of the hydroxy group into a bulky TIPS ether.[23] Indeed subjection of TIPS ether **17** to the conditions of the directed rhodium-catalyzed hydroformylation sets the stereocenter (d.r. = 95:5) at C6 with concomitant formation of aldehyde **18**. As control reactions, the benzyl ether **20a** and the corresponding benzoate **20b** were prepared and subjected to the same conditions of hydroformylation, which resulted in no product

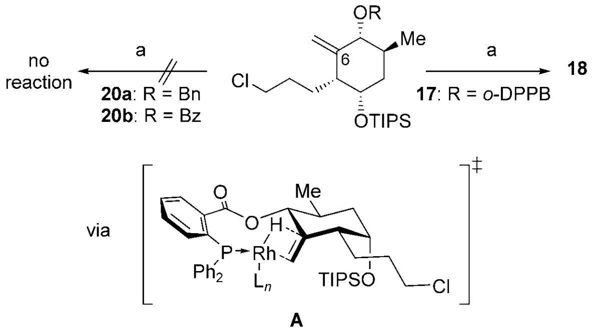


Scheme 5. Synthesis of the central cyclohexane core. Reagents and conditions: a) *o*-DPPBA, DCC, DMAP, CH_2Cl_2, RT, 86 %; b) $[Rh(CO)_2(acac)]$ (2 mol %), H_2/CO (1:1, 40 bar), toluene, 70 °C, 89 %; c) $BF_3{\cdot}OEt_2$, toluene, 70 °C, 85 %; d) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 92 %; e) $[Rh(CO)_2(acac)]$ (2 mol %), $P(OPh)_3$ (8 mol %), H_2/CO (1:1, 20 bar), toluene, 50 °C, 85 %; f) TBAF, $BF_3{\cdot}OEt_2$, THF, RT; 80 %. acac = acetylacetonate, DCC = *N*,*N'*-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, *o*-DPPBA = *ortho*-diphenylphosphanylbenzoic acid, TIPS = triisopropylsilyl, Tf = trifluoromethanesulfonyl.

formation in both cases (Scheme 6). This outcome can be understood in the context that 1,1-disubstituted alkenes are in general rather unreactive for hydroformylation owing to steric hindrance. Hence, in this case these results also prove the role of the *o*-DPPB function as a catalyst-directing group to control both chemo- and diastereoselectivity of this second key hydroformylation step. For rhodium-catalyzed hydroformylation the hydrometalation step is considered to be the rate- and selectivity determining step. Thus, the proposed transition state **A** provides a rational for the observed stereochemistry in this hydroformylation step.[24]



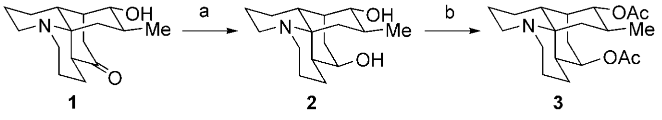
Scheme 7. Final steps for the synthesis of **1**. Reagents and conditions: a) **21**, THF, −20 °C; b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 70% over two steps; c) DIBAH, CH_2Cl_2, −78 °C, 95%; d) Ac_2O, pyridine, 0 °C, 88%; e) NaN_3, NaI, DMSO, 90 °C; 89%; f) TBAF, THF, RT, 95%; g) Dess–Martin periodinane, 80%; h) PPh_3, MeCN/H_2O (4:1); 50 °C; then **26**, toluene, reflux, 70%; i) HBr/HOAc, RT; then NaOH/H_2O (1:1), MeOH, RT, 51%. DIBAH = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide.



Scheme 6. Control experiment and rational for the role of the *o*-DPPB group as a catalyst-directing Group for the hydroformylation of **17**. Reagents and conditions: a) $[Rh(CO)_2(acac)]$ (2 mol%), $P(OPh)_3$ (8 mol%), H_2/CO (1:1, 20 bar), toluene, 50 °C. Bn = benzyl, Bz = benzoyl.

To complete the final carbon skeleton, Grignard reagent **21** was added to aldehyde **18**, and the resulting alcohol was protected as its bis(silyl) ether **22** (Scheme 7).[23] Reductive cleavage of the (*o*-DPPB)-group, and subsequent acetylation furnished chloride **23**. Standard functional group interconversions involving transformation of the chloride group into the azide moiety,[10a] cleavage of both TIPS ether functions,[22] and subsequent oxidation (Dess–Martin periodinane)[25] to the corresponding diketone furnished diketoazide **24** as a single diastereomer. A chemoselective Staudinger/Aza-Wittig[10b] sequence (six- vs. eight-membered ring formation) afforded imine **25**, which was transformed (without isolation) into enolether **27** by in situ generation of HBr.[11] This transformation occurred as a cascade process initiated by Mannich reaction, cleavage of the methyl ether mediated by acid, and final enol ether formation. Treatment of enolether **27** with HBr/HOAc generated bromide **28**, which was directly converted into (+)-clavolonine (**1**) under basic conditions to complete the synthesis.[7]

Reduction of (+)-clavolonine (**1**) with lithium aluminum hydride furnished (−)-deacetylfawcettiine (**2**; Scheme 8). Diacetylation of both hydroxy groups occurred upon treatment with MeLi/Ac_2O and furnished (+)-acetylfawcettiine (**3**).[6]



Scheme 8. Synthesis of (−)-deacetylfawcettiine (**2**) and (+)-acetylfawcettiine (**3**). Reagents and conditions: a) LAH, THF, −78 °C, 80%; b) MeLi, THF, 0 °C; then Ac_2O, RT, 90%. LAH = lithium aluminum hydride.

In conclusion, the total synthesis of (+)-clavolonine (**1**), as well as the first enantioselective synthesis of (−)-deacetylfawcettiine (**2**) and (+)-acetylfawcettiine (**3**) have been completed. The synthesis is another example of making use of efficient substrate direction by way of applying the concept of a CDG-controlled organic synthesis. Thus, the first stereogenic center was generated by asymmetric catalysis, and all remaining five (six) stereogenic centers were exclusively constructed by substrate control. At the heart of the synthesis is a new strategy for the construction of the central cyclohexane core (**7**) consisting of a reaction sequence of (*o*-DPPB)-directed hydroformylation/carbonyl-ene and a second (*o*-DPPB)-directed hydroformylation reaction, thus giving a rapid increase of molecular complexity. It is the first application of such a reaction sequence in the context of complex alkaloid synthesis, and highlights the potential usefulness of a strategy involving CDG-controlled organic synthesis in total synthesis.

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[1] Y. Hirasawa, J. Kobayashi, H. Morita, *Heterocycles* **2009**, *77*, 679.

[2] a) J. Kobayashi, H. Morita, *The Alkaloids, Chemistry and Physiology*, *Vol. 61* (Ed.: R. H. F. Manske), Academic Press, New York, **2005**, p. 1; b) D. B. McLean, *The Alkaloids, Chemistry and Physiology*, *Vol. 10* (Ed.: R. H. F. Manske), Academic Press, New York, **1968**, p. 305.

[3] a) R. H. Burnell, D. R. Taylor, *Chem. Ind.* **1960**, 1239; b) R. H. Burnell, B. S. Mootoo, *Can. J. Chem.* **1961**, *39*, 1090.

[4] a) R. H. Burnell, *J. Chem. Soc.* **1959**, 3091; b) R. H. Burnell, B. S. Mootoo, D. R. Taylor, *Can. J. Chem.* **1960**, *38*, 1927.

[5] a) X. Ma, D. R. Gang, *Nat. Prod. Rep.* **2004**, *21*, 752; b) M. G. Ortega, A. M. Agnese, J. L. Cabrera, *Phytomedicine* **2004**, *11*, 539.

[6] E. Wenkert, C. A. Broka, *J. Chem. Soc. Chem. Commun.* **1984**, 714.

[7] D. A. Evans, J. R. Scheerer, *Angew. Chem.* **2005**, *117*, 6192; *Angew. Chem. Int. Ed.* **2005**, *44*, 6038.

[8] C. Rein, P. Demel, R. A. Outten, T. Netscher, B. Breit, *Angew. Chem.* **2007**, *119*, 8824; *Angew. Chem. Int. Ed.* **2007**, *46*, 8670.

[9] R. H. Burnell, D. R. Taylor, *Tetrahedron* **1961**, *15*, 173.

[10] a) P. H. Lambert, M. Vaultier, R. Carrié, *J. Org. Chem.* **1985**, *50*, 5352; b) M. Vaultier, P. H. Lampert, R. Carrié, *Bull. Soc. Chim. Fr.* **1986**, 83.

[11] a) C. H. Heathcock, E. F. Kleinman, *J. Am. Chem. Soc.* **1981**, *103*, 222; b) C. H. Heathcock, E. F. Kleinman, E. S. Binkley, *J. Am. Chem. Soc.* **1982**, *104*, 1054.

[12] A. Bigot, D. Breuninger, B. Breit, *Org. Lett.* **2008**, *10*, 5321.

[13] a) K. Omura, A. K. Sharma, D. Swern, *J. Org. Chem.* **1976**, *41*, 957; b) A. J. Mancuso, S.-L. Huang, D. Swern, *J. Org. Chem.* **1978**, *43*, 2480.

[14] B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863.

[15] J. M. Schwab, D. C. T. Lin, *J. Am. Chem. Soc.* **1985**, *107*, 6046.

[16] a) E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092; *Angew. Chem. Int. Ed.* **1998**, *37*, 1986; b) J. Garcia, M. López, J. Romeu, *Synlett* **1999**, 429.

[17] The *ee* values was determined by GC analysis on a chiral stationary phase after conversion into the acetate, for details see the Supporting Information.

[18] a) K. A. Parker, Q. Xie, *Org. Lett.* **2008**, *10*, 1349; b) Z. Lu, S. Ma, *J. Org. Chem.* **2006**, *71*, 2655.

[19] a) C. L. Rand, D. E. Van Horn, M. W. Moore, E. Negishi, *J. Org. Chem.* **1981**, *46*, 4093; b) E. Negishi, D. E. Van Horn, T. Yoshida, *J. Am. Chem. Soc.* **1985**, *107*, 6639.

[20] B. Neises, W. Steglich, *Angew. Chem.* **1978**, *90*, 556; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522.

[21] a) B. Breit, *Acc. Chem. Res.* **2003**, *36*, 264; b) B. Breit in *Topics in Organometallic Chemistry*, *Vol. 24* (Ed.: N. Chatani), Springer, Berlin, **2007**, pp. 145–168.

[22] For details see the Supporting Information.

[23] C. Rücker, *Chem. Rev.* **1995**, *95*, 1009.

[24] The relative configuration obtained after carbonyl-ene and hydroformylation reactions was determined by nOe interactions, which were evaluated after conversion into bicyclic enolether **19**.

[25] a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155; b) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277.