Concise Enantiospecific Synthesis of (+)-Calvine

Purnama Dewi-Wülfing, Julian Gebauer, Siegfried Blechert*

Technische Universität Berlin, Institut für Chemie, Strasse des 17. Juni 135, 10623 Berlin, Germany
Fax +49(30)31423619; E-mail: blechert@chem.tu-berlin.de

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Abstract: We report herein an efficient enantiospecific synthesis of (+)-calvine in nine steps from (*R*)-epichlorohydrine. The convergent synthesis is based on an olefin cross-metathesis (CM) reaction of a chiral homoallylamine and an enone. Subsequent reductive cyclization and lactonization of the *cis*-2,6-disubstituted piperidine intermediate furnished the product in good yield.

Key words: olefin cross-metathesis, hydrogenation, lactones, ruthenium catalyst, alkaloids

Ladybird beetles (*Coccinellidae*) are rarely exploited as food sources by predators, owing to toxic alkaloids produced in their hemolymph, which are released as small yellow droplets from their knee joints once they are disturbed or molested.[1] Calvine, a *cis*-2,6-disubstituted piperidine annulated with a seven-membered lactone, is the major alkaloid found in two ladybird beetles *Calvia 10-guttata* and *Calvia 14-guttata*. 2-Epicalvine, its corresponding *trans*-lactone, was also found as the minor constituent (about 10%, Figure 1).

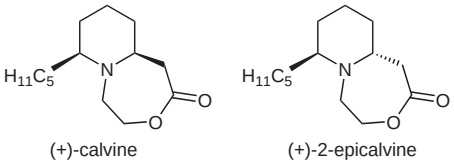

Figure 1 Alkaloids found in *Calvia10- and 14-guttata*

Braekman and coworkers isolated the alkaloids in 1999 and determined their absolute configuration by so far the first and only total synthesis in 2000.[2] They utilized the CN(*R*,*S*) method[3] as the key step to prepare a *cis*-2,6-disubstituted piperidine methyl ester intermediate. The hydroxyethyl group was introduced later in the synthesis by treating the piperidine intermediate with an excess of oxirane in methanol. This step, which was the major drawback of the synthesis, resulted in a complex mixture containing calvine, 2-epicalvine, N-alkylated methyl ester (*cis*/*trans* 1:1) and N,N-dialkylated retro-Michael product. The low selectivity was caused by the interconversion of calvine to 2-epicalvine in protic solvents via transesterification, ring-opening, and retro-Michael reaction. Interestingly, both lactones are stable in aprotic solvents such as THF or acetonitrile.[2]

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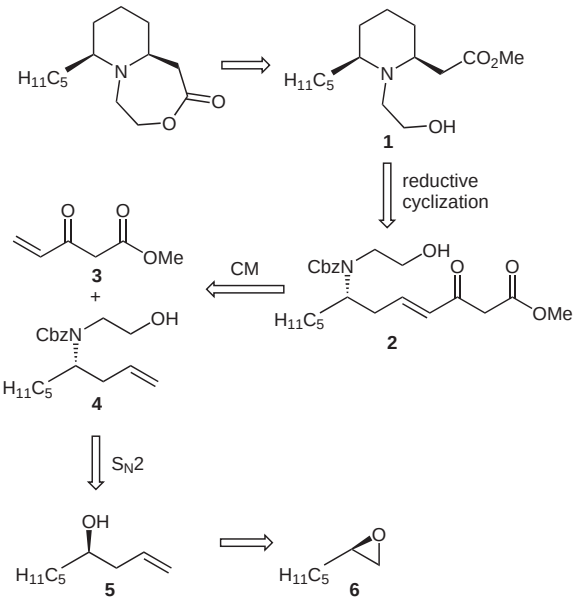
Previous works within our group established the methodology for the synthesis of *cis*-2,6-disubstituted piperidines.[4] We were therefore eager to apply the sequential olefin cross-metathesis–reductive cyclization method to synthesize calvine. In contrast to the synthesis of Braekman, we found it advantageous to introduce the hydroxyethyl group early in the synthesis to avoid the unselective hydroxyethylation. We envisaged the ester **1** as a synthetic precursor, which should result from the reductive cyclization of enone **2**, the CM product of enone **3** and enantiopure homoallylamine **4**. The homoallylamine should be prepared via substitution of homoallylalcohol **5**, in turn available from oxirane **6** (Scheme 1). To avoid the interconversion of calvine to 2-epicalvine, careful selection of the reaction solvents was crucial.



Scheme 1 Retrosynthetic analysis of calvine

The synthesis of calvine is presented in Scheme 2. The CM partner **3** was prepared in two steps according to the procedure of Zibuck and Streiber.[5] The aldol reaction of methyl acetate and acrolein occurred smoothly to furnish the allyl alcohol **7**. The Jones oxidation yielded after Kugelrohr distillation the desired enone **3** in 55% yield.

The CM partner **4** should be prepared from an enantiopure homoallylalcohol. Brown and coworkers reported the reaction between allyldiisopinocampheylborane and *n*-butyraldehyde to furnish (*R*)-hept-1-en-4-ol in 72% yield with moderate 87% ee.[6] Another approach was the

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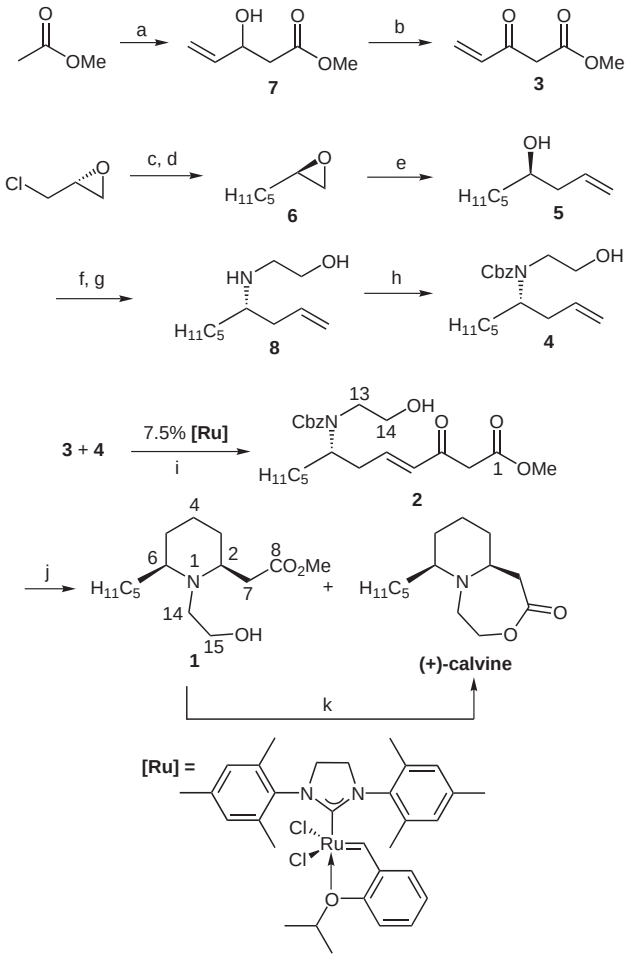
Barbier reaction between allyltributyltin and hexanal in the presence of a catalytic amount (20 mol%) of a chiral BINOL–$TiCl_2$ complex to give (*R*)-non-1-en-4-ol in 75% yield and 98.4% ee. However, the reaction was reported on small scale (1.5 mmol of aldehyde) and elaborate technique was required to prepare the chiral complex.[7] An alternative method was reported by Fürstner and coworkers, which involved an oxirane opening by vinylmagnesium bromide in the presence of catalytic amounts of CuCl(COD) (COD = cyclooctadiene). This method is suitable for large scale and does not result in any erosion of ee.[8]



Scheme 2 *Reagents and conditions*: (a) LDA, THF, –78 °C; acrolein, 5 min, quant.; (b) CrO_3, H_2SO_4, acetone, 18 h, 55%; (c) *n*-BuMgCl, CuCN (10 mol%), –78 °C to 0 °C, 2.5 h, quant.; (d) NaOH, THF–H_2O, 20 h, 87%; (e) vinylMgBr, CuCN (10 mol%), –78 °C to r.t., 24 h, 84%; (f) TsCl, DMAP (10 mol%), CH_2Cl_2, 7 d, 72%; (g) ethanolamine, THF, reflux, 6 d, 77%; (h) CbzCl, K_2CO_3, H_2O–CH_2Cl_2, 4 h, 73%; (i) **3** (2 equiv), **4** (1 equiv), [Ru] (7.5 mol%), CH_2Cl_2, reflux, 18 h, 70%; (j) 10% Pd/C, *i*-Pr_2O, 3 bar H_2, 40 °C, 3 d, 61% **1** and 13% calvine; (k) PTSA (1.1 equiv), benzene, reflux, 18 h, 66%.

The homoallyalamine **4** was prepared in six steps, starting from (*R*)-epichlorohydrine. Its conversion to pentyl oxirane **6** was done by copper-catalyzed oxirane opening with *n*-butyl magnesium chloride followed by oxirane formation in basic conditions.[9] Successive oxirane opening with vinyl magnesium bromide gave the homoallylalcohol **5** in 84% yield.[10,11] Copper cyanide works as well as CuCl(COD) in catalyzing the reaction. The transformation of homoallylalcohol **5** to homoallylamine **4** was accomplished by tosylation, nucleophilic substitution, and introduction of the Cbz protecting group, yielding the homoallylamine **4**. The tosylation proceeded slowly and was complete after seven days. The substitution reaction was complete after six days yielding the volatile homoallylamine **8**. The benzyloxycarbonylation was done in a two-phase reaction system, which gave solely the N-protected homoallylamine. We expected that the substitution reaction occurred with complete inversion of configuration (S_N2 mechanism). As we could not determine the configuration of **8** or **4** either via chiral HPLC or Mosher derivatives, we decided to continue our synthesis since the configuration of the final product would provide more information about the substitution reaction.

CM between enone **3** and homoallylamine **4** was conducted in the presence of 7.5 mol% Hoveyda–Blechert ruthenium catalyst [Ru][12] to afford exclusively the *E*-enone **2** in 70% yield.[13] The catalyst was chosen as it shows higher reactivity and stability than the second generation Grubbs' catalyst.[14]

We then investigated the reductive cyclization reaction of enone **2**. Suitable aprotic solvent was required for the reaction as the hydrogenation with methanol as solvent resulted in the epimerization due to the retro-Michael reaction. Reaction in THF led only to the hydrogenation of the double bond with retention of the *N*-Cbz protecting group.[15] Maki and coworkers reported a hydrogenation reaction with various solvents, in which isopropyl ether proved to be as effective as methanol in hydrogenating benzyl ester moiety.[16] Conducting the reductive hydrogenation in isopropyl ether at 3 bar of hydrogen and 40 °C for three days afforded a mixture of the *cis*-2,6-disubstituted piperidine **1** and calvine in 61% and 13% yields, respectively.[17,18] Both products were chromatographically separated and the piperidine **1** was subjected to lactonization conditions.

Braekman and coworkers reported a lactonization procedure, in which the crude mixture resulted from hydroxyethylation was heated in acetonitrile at 50 °C in the presence of Amberlyst A15 and molecular sieve.[2] Using this procedure calvine was obtained in 60% yield together with 25% recovered piperidine **1**. We found out that the TLC controls detected only the substances in the solution. The adduct attached on the Amberlyst surface remained undetected and it was released only during workup, giving low yield and conversion. A complete conversion was achieved by treating the piperidine **1** with a slight excess of *p*-toluenesulfonic acid in refluxing benzene, affording neat calvine in 66% yield.[19,20] The spectral data and optical rotation of the final product were in agreement to the reported values. The enantiopurity of calvine also confirmed the complete inversion of configuration of the crucial nucleophilic substitution reaction.

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In summary, we have performed an enantioselective synthesis of (+)-calvine in nine steps starting from (*R*)-epichlorohydrine with an overall yield of 10%. The key strategies included the copper-catalyzed oxirane opening, S_N2 reaction, and sequential CM–reductive cyclization method. Further investigations and syntheses based on this concept are currently under study in our laboratories and the results will be reported in due course.

Acknowledgment

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(10) The optical rotation of the product $[\alpha]_D^{20}$ +8.7 (*c* 1.4, $CHCl_3$) was in agreement with the reported value {lit.[11] $[\alpha]_D^{25}$ +8.3 (*c* 1.4, $CHCl_3$)}.

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(13) **Preparation and Selected Data of Enone 2.**
[Ru] (11 mg, 18 μmol) was added to a solution of homoallylamine **4** (76 mg, 0.2 mmol) and enone ester **3** (60 mg, 0.4 mmol) in anhyd CH_2Cl_2 (4.7 mL) under a nitrogen atmosphere. The mixture was heated at reflux for 20 h. The solvent was evaporated and the residue was purified by column chromatography (SiO_2, cyclohexane–EtOAc 3:2) to give **2** (70 mg, 70%, as keto–enol mixture) as a brown oil. $[\alpha]_D^{20}$ –8.0 (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.81 (br s, 3 H, H-12), 1.20 (br s, 8 H, H-9–11), 1.45–1.59 (m, 2 H, H-8), 2.20–2.68 (m, 2 H, H-6), 3.29 (br s, 2 H, H-13), 3.45 (s, H-2 keto), 3.50 (br s, 2 H, H-14), 3.68, 3.70 (s, 3 H, OCH_3), 4.05 (br s, 1 H, H-7), 4.96 (s, H-2 enol), 5.12 (s, 2 H, H-16), 5.69–5.85 and 6.05–6.20 (m, 1 H, H-4), 6.45–6.62 and 6.69–6.86 (m, 1 H, H-5), 7.21–7.41 (br s, 5 H, Ar), 11.75 (s, OH enol) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0 (C-12), 22.6 (C-11), 26.1 (C-10), 31.6 (C-9), 33.1, 33.4 (C-8), 36.5, 37.0 (C-6), 46.4, 46.7 (C-13), 51.3 (C-7), 52.4 (OMe), 61.6, 62.6 (C-14), 67.2, 67.8 (C-15), 90.5 (C-2), 126.6 (C-4), 1276.9, 128.1, 128.3, 128.7, 131.3, 136.8 (Ar), 145.9, 147.0 (C-5), 155.6 (C-16), 173.3 (C-1), 191.7 (C-3) ppm.

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(18) **Preparation and Selected Data of Piperidine 1.**
Cross-metathesis product **2** (270 mg, 0.64 mmol) in isopropyl ether (20 mL) was hydrogenated over 10% Pd/C (68 mg, 60 μmol) at 3 bar and 40 °C for 3 d. After filtration over Celite® and evaporation, the residue was purified by column chromatography (SiO_2, CH_2Cl_2–MeOH–NH_3 97:3:0.1) to afford piperidine **1** (105 mg, 61%) and calvine (20 mg, 13%) as a light-yellow oil. $[\alpha]_D^{20}$ +8.5 (*c* 1.3, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7 Hz, 3 H, H-13), 1.10–1.80 (m, 14 H, H-3–5,9–12), 2.39 (dd, *J* = 15, 9 Hz, 1 H, H-7), 2.51–2.77 (m, 4 H, H-6,7,14), 3.09–3.25 (m, 1 H, H-2), 3.46 (t, *J* = 6 Hz, 2 H, H-15), 3.68 (s, 3 H, OCH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (C-13), 21.7 (C-4), 22.7 (C-12), 26.2 (C-3), 27.0 (C-10), 27.3 (C-5), 32.1 (C-11), 34.1 (C-9), 39.3 (C-7), 48.4 (C-14), 51.7 (OMe), 58.3 (C-2), 60.5 (C-15), 61.9 (C-6), 173.0 (C-8) ppm.

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(20) **Preparation and Selected Data of (+)-Calvine.**
To a solution of **1** (12 mg, 44 μmol) in benzene (3 mL), *p*-TSA monohydrate (9.2 mg, 48 μmol) was added and the mixture was heated at reflux under a nitrogen atmosphere for 18 h. Then, CH_2Cl_2 (10 mL) and sat. aq $NaHCO_3$ solution (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the collected organic layers were evaporated to give neat calvine (7 mg, 66%) as a light-yellow oil. $[\alpha]_D^{20}$ +18.3 (*c* 0.35, CH_2Cl_2) {lit.[2] $[\alpha]_D^{20}$ +18 (*c* 0.66, CH_2Cl_2)}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7 Hz, 3 H, H-13), 1.15–1.81 (m, 14 H, H-3–5,9–12), 2.19–2.89 (m, 5 H, H-6,7,14), 3.23–3.37 (m, 1 H, H-2), 4.21–4.36 (m, 2 H, H-15) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (C-13), 21.5 (C-4), 22.7 (C-12), 24.6 (C-3), 25.2 (C-5), 32.3 (C-10, 11), 34.2 (C-9), 43.2 (C-7), 53.5 (C-14), 59.0 (C-2), 62.8 (C-6), 69.0 (C-15), 174.7 (C-8) ppm.

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