Tetrahedron 66 (2010) 2351–2355

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 2,6-disubstituted piperidine alkaloids from ladybird beetles Calvia 10-guttata and Calvia 14-guttata

Peter Kubizna [a], Ivan Špánik [b], Jozef Kožíšek [c], Peter Szolcsányi [a,*]

[a] Department of Organic Chemistry, Slovak University of Technology, Radlinského 9, SK-812 37 Bratislava, Slovakia
[c] Department of Analytical Chemistry, Slovak University of Technology, Radlinského 9, SK-812 37 Bratislava, Slovakia
[b] Department of Physical Chemistry, Slovak University of Technology, Radlinského 9, SK-812 37 Bratislava, Slovakia

ARTICLE INFO

Article history:
Received 27 October 2009
Received in revised form 18 December 2009
Accepted 27 January 2010
Available online 2 February 2010

Keywords:
Palladium
Carbonylation
Amino alcohols
Heterogeneous catalysis
Natural products

ABSTRACT

Optically pure (+)-calvine, (+)-2-epicalvine, (2*S*,6*S*)-(6-pentylpiperidin-2-yl)acetic acid methyl ester and (2*R*,6*S*)-(6-pentylpiperidin-2-yl)acetic acid methyl ester, four piperidine alkaloids isolated from ladybird beetles of the genus Calvia (Coccinellidae), were synthesised from a common precursor using cyclisative Pd(II)/Cu(II)-catalysed carboamination-(methoxy)carbonylation tandem reaction of alkenylamines as a key step. The first single-crystal X-ray analysis of (+)-calvine confirmed its proposed absolute configuration to be (2*S*,6*S*) corresponding to that of natural product.

1. Introduction

Insects use various toxic molecules as chemical weapons to discourage potential predators.[1] It is known that coccinellid beetles often release small droplets of yellow hemolymph at their knee joints, when molested or disturbed (so called 'reflex bleeding').[2] As a consequence, these insects are only rarely exploited as a food source by other organisms, which is attributed to the presence of deterrent compounds in their blood.[3] Among them, piperidine alkaloids represent a prominent class of such natural products displaying defensive properties.[4]

Recently, four 2,6-disubstituted piperidine alkaloids (+)-calvine **1**, (+)-2-epicalvine **2**, (2*S*,6*S*)-(6-pentylpiperidin-2-yl)acetic acid methyl ester **3** and (2*R*,6*S*)-(6-pentylpiperidin-2-yl)acetic acid methyl ester **4**, were isolated from two species of ladybird beetles Calvia 10-guttata and Calvia 14-guttata (Coccinellidae)[5] (Fig. 1). To the best of our knowledge, no biological activity of these alkaloids has been determined so far.

The structure and relative configuration of **1**–**4** was established on the basis of NMR spectroscopy and HRMS studies and subsequently confirmed via racemic total synthesis.[5] The absolute configuration was determined by enantioselective total synthesis.[6] Since then, only one other preparation of **1** has appeared[7] along with two formal syntheses.[8] All but one approach known so far used alkaloids **3** and/or **4** as key intermediates for the (formal) syntheses of **1** and/or **2**.[5,6,8] Recently, we have communicated racemic syntheses of calvine and epicalvine.[9] In this full account, we wish to report short and efficient stereoselective total syntheses of all four naturally occurring piperidine alkaloids **1**–**4**. Our approach relies on diastereoselective intramolecular Pd(II)/Cu(II)-catalysed tandem aminocyclisation–carbonylation reaction of alkenylamines **5** and/or **6** as a key step, while both these substrates were prepared from the common precursor **7** (Scheme 1).

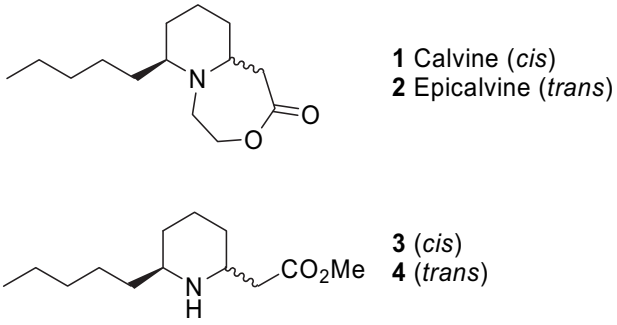
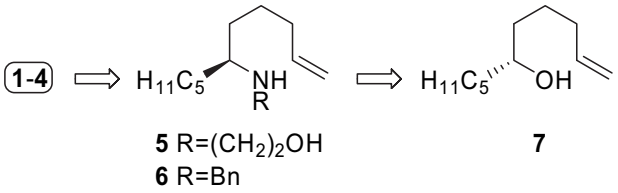


Figure 1. Piperidine alkaloids isolated from Calvia ladybird beetles.

* Corresponding author.
E-mail address: peter.szolcsanyi@stuba.sk (P. Szolcsányi).

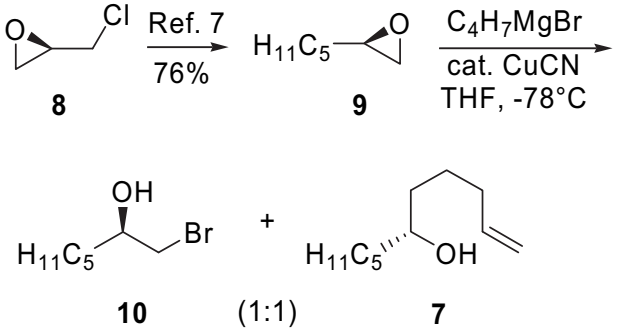
0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.01.106



Scheme 1. Retrosynthetic analysis of alkaloids **1**–**4**.

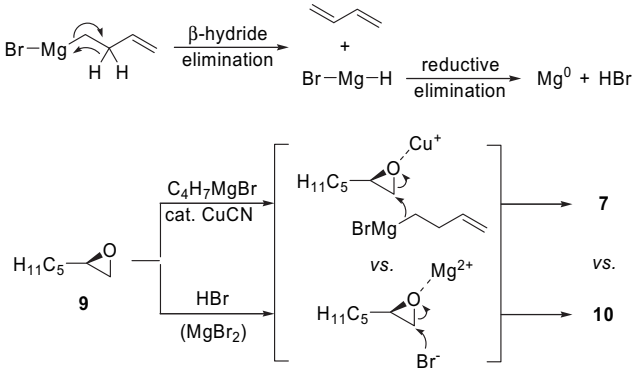
2. Results and discussion

Initial preparation of both substrates **5** and **6** needed for the key Pd(II)-catalysed cyclisation started from the commercially available (*R*)-epichlorohydrin **8** (Scheme 2). Our intention was to transform it to (*R*)-undec-1-en-6-ol **7** via double-ring opening of the epoxide using an 'alkylation first–alkenylation second' sequence. However, such strategy surprisingly failed to provide the desired alcohol **7** in a reasonable yield even after extensive experimentation. While the CuCN-catalysed ring opening of **8** with butylmagnesium bromide and subsequent base–promoted ring closure[10] of crude chlorohydrin afforded the desired (*R*)-pentyloxirane **9**[7] in 76% yield over two steps, the following and analogous opening of the epoxide **9** with butenylmagnesium bromide[11] was unsatisfactory. It gave at best a mixture of the undesired bromohydrin **10** and the desired alcohol **7** (in ratios ranging from 3:1 (Et_2O) to 1:1 (THF)) or complex reaction mixtures only (Scheme 2).



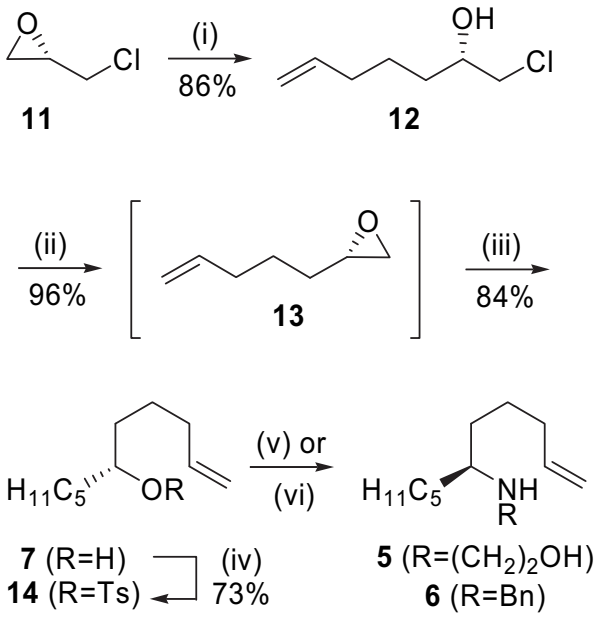
Scheme 2. Initially attempted preparation of alcohol **7**.

We speculated, that the formation of the undesired bromohydrin **10** from the epoxide **9** is due to the competitive attack of the Br^- nucleophile from in situ formed HBr (and/or $MgBr_2$). This may come from the β-hydride elimination of butenylmagnesium bromide generating 1,3-butadiene followed by reductive elimination of the magnesium hydride complex. This hypothesis is supported by the experimental observation that grey precipitate (possibly metallic Mg) is gradually deposited on the glassware during the course of reaction (Scheme 3).[12]



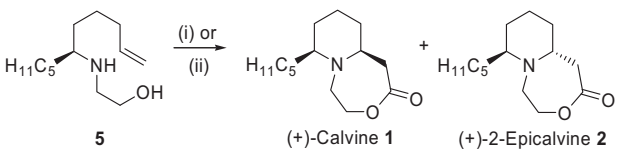
Scheme 3. Proposal for the formation of undesired bromohydrin **10**.

Thus, we had to reverse the order of double-ring opening transformation and conducted the 'alkenylation first–alkylation second' sequence on the (*S*)-epichlorohydrin **11**. This substrate was initially opened with butenylmagnesium bromide and the resulting chlorohydrin **12** subsequently closed under basic conditions to the unsaturated epoxide **13**.[13] Gratifyingly, the following addition of excess butyllithium catalysed by copper(I) iodide afforded the desired alcohol **7**[14] in 70% combined yield over three steps. Activation of the hydroxyl group of **7** using TsCl gave tosylate **14**, which was treated either with excess ethanolamine to yield the unsaturated amino alcohol **5**[15] or with excess benzylamine to provide the corresponding alkenylamine **6** (Scheme 4).



Scheme 4. Optimised preparation of substrates **5** and **6**. Reagents and conditions: (i) 1.5 equiv butenylmagnesium bromide, 0.15 equiv CuI, THF, −50 °C to rt, 16 h, 86%; (ii) 11 equiv NaOH, THF/H_2O (1/1), rt, six days, 96%; (iii) 2.2 equiv butyllithium, 0.2 equiv CuI, Et_2O, −78 °C to rt, 2.5 h, 84%; (iv) 1.2 equiv TsCl, 19 equiv pyridine, CH_2Cl_2, 0 °C to rt, 40 h, 73%; (v) 15 equiv ethanolamine, THF, reflux, 40 h, 91%; (vi) 3 equiv benzylamine, THF, reflux, eight days, 81%.

With both substrates in hand, we subjected them to the final key transformation. Under optimal reaction conditions,[16] the Pd(II)/Cu(II)-catalysed aminocyclisation–lactonisation[17] of **5** directly provided the desired target alkaloids (+)-calvine **1** and (+)-2-epicalvine **2** in a diastereoselective fashion depending upon the applied catalytic conditions. Thus, using $PdCl_2$ as a catalyst and excess $CuCl_2$ as reoxidant we obtained **1** as a major product in a diastereomeric ratio of 2.2:1 and 18% yield over six steps.[9] On the other hand, the combination of molecular oxygen (1 atm) with catalytic copper(II) chloride as reoxidant system afforded the diastereomeric (+)-2-epicalvine **2** as a major product in a ratio of 7:3 resulting in the overall yield of 17% in six steps (Scheme 5).



Scheme 5. Finalisation and the key step of the total synthesis of (+)-calvine **1** and (+)-2-epicalvine **2**. Reagents and conditions: (i) CO (balloon), 0.1 equiv $PdCl_2$, 2 equiv $CuCl_2$, 2 equiv AcONa, dioxane, 40 °C, 7 h, 55% (**1**/**2**=2.2/1); (ii) CO/O_2 (ca. 1:1, balloon), 0.1 equiv $PdCl_2$, 0.2 equiv $CuCl_2$, 3 Å molecular sieves, dioxane, 50 °C, 45 h, 53% (**1**/**2**=3/7).

So far, the exact structure of the true catalytic species involved in our Pd(II)/Cu(II)-catalysed aminocyclisation–lactonisation of **5** remains unclear. However, due to the metal composition of optimal reaction conditions it inevitably should be of a heterobimetallic nature. Such Pd/Cu-complexes in analogous transformations involving both palladium and copper salts have been proposed and/or isolated and characterised.[18]

After the convenient FLC separation of both diastereomers **1** and **2**, the enantiomerically pure (+)-calvine **1** turned out to be a crystalline compound.[19] The first single-crystal X-ray analysis of **1**[20] confirmed its proposed absolute configuration to be (2*S*,6*S*) corresponding to that of the natural product. Moreover, it can be seen that both piperidine and lactone rings adopt chair-like conformation in the solid state (Fig. 2).

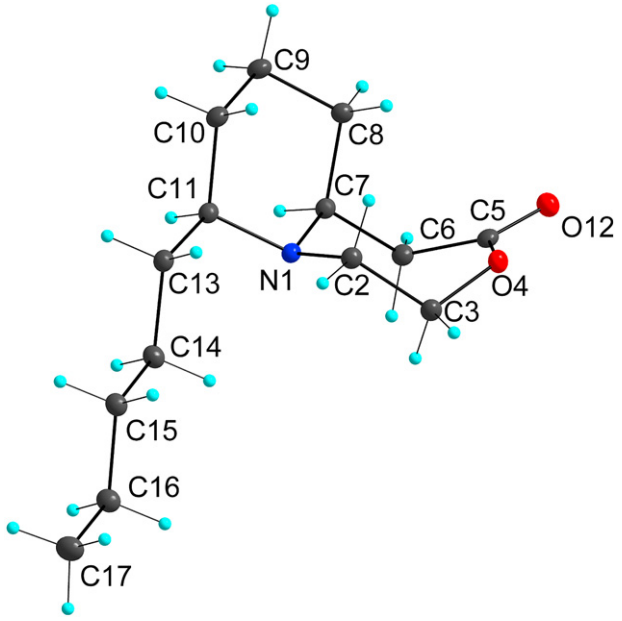
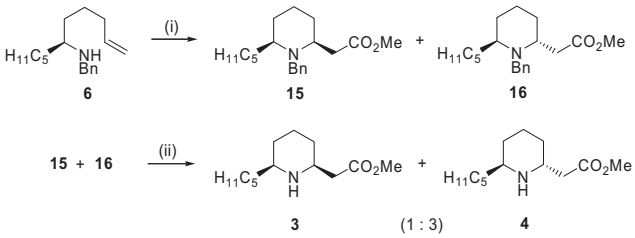


Figure 2. An ORTEP view of the crystal structure of natural (+)-calvine **1**.

In order to finalise the total synthesis of the other two target alkaloids **3** and **4**, we subjected alkenylamine **6** to the Pd(II)/Cu(II)-catalysed aminocyclisation–methoxycarbonylation sequence.[17e,21] As the cyclisative preparation of *trans*-2,6-disubstituted piperidines bearing an ester group in the β-position is more challenging[22] in comparison to their *cis*-counterparts, we have focused particularly on the conditions favouring the formation of the former one.[23] Thus, exposure of **6** to catalytic $PdCl_2$ and $CuCl_2$ in MeOH under the CO/O_2 atmosphere afforded an inseparable mixture of the desired piperidines **15**/**16** in the 68% combined yield. The final catalytic debenzylation of methylesters **15**/**16** on Pearlman's catalyst provided easily separable target alkaloids **3** and **4** in 81% combined yield and in a ratio of 1:3 in favour of the 2,6-*trans*-configured piperidine **4**[24] (Scheme 6).



Scheme 6. Key step and finalisation of the total synthesis of **3** and **4**. Reagents and conditions: (i) CO/O_2 (ca. 1:1, balloon), 0.1 equiv $PdCl_2$, 0.2 equiv $CuCl_2$, 3 Å molecular sieves, MeOH, rt, 18 h, 68%; (ii) H_2 (balloon), 0.2 equiv $Pd(OH)_2$, MeOH, rt, 24 h, 81% (**3**/**4**=1/3).

3. Conclusion

We synthesised four optically pure alkaloids (+)-calvine **1**, (+)-2-epicalvine **2**, (2*S*,6*S*)-(6-pentylpiperidin-2-yl)acetic acid methyl ester **3** and (2*R*,6*S*)-(6-pentylpiperidin-2-yl)acetic acid methyl ester **4** using intramolecular Pd(II)/Cu(II)-catalysed aminocyclisation–carbonylation tandem reaction as a key step. Both necessary alkenylamines **5** and **6** required for these crucial transformations were efficiently prepared in five steps starting from the common substrate (*S*)-epichlorohydrin in 46% and 41% overall yields, respectively. By tuning the reaction parameters we were able to direct the stereoselectivity of the respective Pd(II)/Cu(II)-catalysed cyclisations in order to obtain either diastereomer of target natural compounds **1**–**4**. Thus, using catalytic $PdCl_2$ and excess $CuCl_2$ we obtained 2,6-*cis*-configured alkaloid **1** as a major product in 18% overall yield in six steps. On the other hand, the combination of molecular oxygen with catalytic $PdCl_2$ and $CuCl_2$ afforded both 2,6-*trans*-configured alkaloids **2** and **4** as main adducts in 17% and 13% overall yields. Finally, we have performed the first single-crystal X-ray analysis of (+)-calvine **1** and confirmed its proposed absolute configuration to be (2*S*,6*S*) corresponding to that of the isolated natural product.

4. Experimental section

4.1. General

All solvents were distilled before use: diethylether, THF and dioxane from Na/benzophenone, MeOH from MeONa and CH_2Cl_2 from P_2O_5. Thin layer chromatography (TLC) was performed on aluminium plates pre-coated with 0.2 mm silica gel 60 F_{254} (Merck). Flash column liquid chromatography (FLC) was performed on Kieselgel 60 (40–63 μm). GC was performed on HP-5 column (30 m, ID 0.25 mm, film thickness 0.12 μm) equipped with split/splitless injector and FID detector. Optical rotations were measured with a Perkin–Elmer 241 polarimeter with a 1.000 cm cell at λ=589 nm. Elemental analyses were performed by the Microanalytical Service of Slovak Academy of Sciences. Infrared (IR) spectra were recorded on a Nicolet 5700 FTIR spectrometer. X-ray analysis was performed on Oxford Diffraction GEMINI R diffractometer. Melting point was determined on BÜchi B-540 apparatus. NMR spectra were recorded on Varian VXR-300 (300 MHz) and Inova 600 (600 MHz) spectrometers, respectively. Chemical shifts (δ) are quoted in parts per million and the residual protic solvent was used as internal reference. The COSY and NOESY techniques were used in assignment of ^1H–^1H relationships and the determination of relative configuration. The multiplicities of carbons were assigned from a broadband decoupled analysis used in conjunction with APT. The HMBC technique was used throughout for the assignment of the ^1H–^{13}C relationships.

*4.1.1. (S)-1-Chlorohept-6-en-2-ol (**12**).* To a cooled freshly prepared THF solution (0.96 M) of butenylmagnesium bromide (1.5 equiv) [made of Mg turnings (2.339 g, 96.23 mmol) and butenyl bromide (13.392 g, 10.07 mL, 96.23 mmol) in dry THF (100 mL)] was added anhydrous CuI (1.833 g, 0.15 equiv) at −50 °C in one portion under Ar. After 5 min stirring, while the colour of the mixture changed from grey to deep turqoise, the solution of (*S*)-epichlorohydrin **11** (5.936 g, 5.03 mL, 64.15 mmol) in dry THF (50 mL) was added dropwise via syringe at −50 °C over 20 min under Ar. The resulting deep-blue mixture was left to stir for 16 h while the temperature gradually rose to 25 °C over the indicated time. The reaction was then quenched by addition of satd aq NH_4Cl solution (350 mL) and water (200 mL). After 30 min stirring, the mixture was extracted with Et_2O (2×150 mL), combined organic extracts were dried over

anhydrous Na_2SO_4, filtered and concentrated in vacuo. The resulting brownish oil (9.54 g) was subjected to FLC (390 g SiO_2, 6×28 cm, ethyl acetate/hexanes=1/5) yielding pure chlorohydrin **12** (8.196 g, 86%) as a pale-yellow oil.

Compound **12**: R_f=0.35 (ethyl acetate/hexanes=1/6); $[\alpha]_D^{15}$ +2.4 (*c* 0.502, CH_2Cl_2); IR (film): ν/cm^{-1}=737, 911, 994, 1038, 1064, 1433, 1640, 2861, 2932, 3361 (br); ^1H NMR (300 MHz, $CDCl_3$): 1.40–1.64 (m, 4H, 3-H, 4-H), 2.04–2.13 (m, 2H, 5-H), 2.23 (d, 1H, *J*=4.1 Hz, exchange with D_2O, OH), 3.47 (dd, 1H, $J_{1a,2}$=7.1, J_{gem}=14.1, 1-H_a), 3.63 (dd, 1H, $J_{1b,2}$=3.2, J_{gem}=14.1, 1-H_b), 3.73–3.87 (br s, 1H, 2-H), 4.94–5.05 (m, 2H, 7-H), 5.79 (tdd, 1H, *J*=6.6, 10.2, 16.8 Hz, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$): 24.8 (CH_2, 4-C), 33.6 (2×CH_2, 3-C, 5-C), 50.6 (CH_2, 1-C), 71.3 (CH, 2-C), 115.0 (CH_2, 7-C), 138.3 (CH, 6-C). $C_7H_{13}ClO$ (148.63): calcd C 56.57, H 8.82, Cl 23.85, O 10.7; found: C 56.38, H 8.97, Cl 23.81, O 10.84%.

*4.1.2. (R)-Undec-1-en-6-ol (**7**).* Chlorohydrin **12** (1 g, 6.73 mmol) was dissolved in THF (10 mL) and 0.3 M solution of NaOH (3 g, 75 mmol, 11 equiv) in H_2O (10 mL) was added. The mixture was stirred at 25 °C for six days to ensure the complete conversion. Then, mixture was diluted with Et_2O (5 mL) and phases were separated. The water layer was extracted with Et_2O (10 mL), combined organic extracts dried over anhydrous Na_2SO_4, filtered and carefully concentrated in vacuo (300 mbar, 35 °C) to ca. 1/10-th of volume. The obtained THF solution (1.187 g) contained highly volatile (*S*)-2-pent-4′-enyl-oxirane **13** (727 mg, 96%) that was shown to be essentially pure by NMR analysis of an aliquot sample. Such THF solution containing crude epoxide **13** (710 mg, 6.333 mmol) was diluted with anhydrous Et_2O (10 mL) and dry CuI (241 mg, 1.267 mmol, 0.2 equiv) was added. The mixture was cooled to −78 °C and 2.1 M solution of *n*-BuLi in hexanes (6 mL, 12.67 mmol, 2 equiv) was added slowly dropwise. The colour has changed from pale yellow to dark blue over 10 min. The mixture was left to stir for 2.5 h while the temperature gradually rose to 20 °C over the indicated time. The reaction was quenched by addition of satd aq NH_4Cl solution (40 mL). After 10 min. stirring, the layers were separated and water phase was extracted with Et_2O (50 mL). Organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo yielding crude alcohol **7** as yellowish oil (900 mg, 84%) that was essentially pure by NMR. An aliquot sample was subjected to FLC (SiO_2, ethyl acetate/hexanes=1/4) to obtain analytically pure alcohol **7** as a pale-yellow oil.

Compound **13**: R_f=0.8 (ethylacetate/hexanes=1/4); IR (film): ν/cm^{-1}=639, 829, 856, 909, 993, 1132, 1259, 1410, 1441, 1457, 1483, 1641, 2560, 2927, 2978; ^1H NMR (300 MHz, $CDCl_3$): 1.50–1.60 (m, 4H, 1′-H, 2′-H), 2.07–2.15 (m, 2H, 3′-H), 2.47 (dd, 1H, $J_{2,3a}$=2.8, J_{gem}=5.1 Hz, 3-H_a), 2.75 (dd, 1H, $J_{2,3b}$=4.0, J_{gem}=5.1 Hz, 3-H_b), 2.88–2.94 (m, 1H, 2-H), 4.94–5.06 (tdd, 2H, 5′-H), 5.80 (tdd, 1H, *J*=6.6, 10.1, 16.8 Hz, 4′-H); ^{13}C NMR (75 MHz, $CDCl_3$): 25.2 (CH_2, 2′-C), 31.9, 33.4 (2×CH_2, 1′-C, 3′-C), 47.1 (CH_2, 3-C), 52.2 (CH, 2-C), 114.8 (CH_2, 5′-C), 138.3 (CH, 4′-C).

Compound **7**: R_f=0.65 (ethylacetate/hexanes=1/4); $[\alpha]_D^{15}$ −1.5 (*c* 3.087, CH_2Cl_2). All other physico-chemical data are identical with those reported for its (*S*)-enantiomer, see Ref. 14.

*4.1.3. (R)-Toluene-4-sulfonic acid 1-pentyl-hex-5-enyl ester (**14**).* To the solution of crude alcohol **7** (6.2 g, 36.432 mmol) in dry CH_2Cl_2 (100 mL) was added anhydrous pyridine (67.6 mL, 0.831 mol, 19 equiv). The mixture was cooled to 0 °C and TsCl (8.333 g, 43.719 mmol, 1.2 equiv) was added portionwise. The solution was stirred at 25 °C over 40 h, diluted with Et_2O (100 mL) and washed with satd aq $CuSO_4$ solution (2×500 mL). The combined water layers were extracted with Et_2O (2×200 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The resulting oil (10.22 g) was subjected to FLC (410 g SiO_2, 6×30 cm, ethyl acetate/hexanes=1/4) yielding pure tosylate **14** (8.508 g, 73%) as a pale-yellow oil.

Compound **14**: R_f=0.59 (ethyl acetate/hexanes=1/4); $[\alpha]_D^{15}$ +4.3 (*c* 1, CH_2Cl_2). $C_{18}H_{28}O_3S$ (324.48): calcd C 66.63, H 8.70, O 14.79, S 9.88; found: C 66.70, H 8.44, O 14.92, S 10.06%. All other physico-chemical data are identical with those obtained for its racemate, see Ref. 9.

*4.1.4. (S)-2-(1-Pent-hex-5-enylamino)-ethanol (**5**).* The solution of tosylate **14** (1.537 g, 4.74 mmol) and ethanolamine (4.343 g, 4.3 mL, 71.1 mmol, 15 equiv) in dry THF (20 mL) was refluxed at 80 °C under condenser over 40 h. The reaction mixture was cooled, diluted with Et_2O (100 mL) and washed with satd aq $NaHCO_3$ solution (50 mL). Separated water layer was extracted with Et_2O (2×50 mL), combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The resulting oil (1.437 g) was subjected to FLC (58 g SiO_2, 4×11 cm, ethyl acetate containing 2% aq NH_4OH) yielding pure amino alcohol **5** (917 mg, 91%) as a pale-yellow oil.

Compound **5**: R_f=0.29 (ethyl acetate containing 2% aq NH_4OH); $[\alpha]_D^{15}$ +1.5 (*c* 0.74, CH_2Cl_2). $C_{13}H_{27}NO$ (213.36): calcd C 73.18, H 12.76, N 6.56, O 7.50; found: C 73.23, H 12.70, N 6.52, O 7.55%. All other physico-chemical data are identical with those obtained for its racemate, see Ref. 9.

*4.1.5. (S)-Benzyl-(1-pentyl-hex-5-enyl)-amine (**6**).* The solution of tosylate **14** (2 g, 6.17 mmol) and benzylamine (2 g, 2 mL, 18.5 mmol, 3 equiv) in dry THF (25 mL) was refluxed at 85 °C under condenser over eight days. The reaction mixture was cooled, diluted with H_2O (50 mL) and extracted with Et_2O (2×20 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The resulting oil (2.136 g) was subjected to FLC (85 g SiO_2, 6×12 cm, gradient elution: ethyl acetate/hexanes=1/10 containing 1% aq NH_4OH–ethyl acetate/hexanes=1/1 containing 1% aq NH_4OH) yielding pure aminoalkene **6** (1.3 g, 81%) as a pale-yellow oil.

Compound **6**: R_f=0.45 (ethyl acetate/hexanes=1/4); $[\alpha]_D^{15}$ +1.5 (*c* 0.74, CH_2Cl_2); IR (film): ν/cm^{-1}=698, 733, 910, 993, 1028, 1073, 1099, 1147, 1377, 1455, 1495, 1641, 2857, 2928, 3390 (br); ^1H NMR (300 MHz, $CDCl_3$): 0.89 (t, 3H, 5′-H′), 1.24–1.48 (m, 12H, 1′-H, 2-H, 2′-H′, 3-H, 3′-H, 4′-H), 1.65 (br s, 1H, exchange with D_2O, NH), 2.00–2.13 (m, 2H, 4-H), 2.52–2.60 (m, 1H, 1-H), 3.76 (s, 2H, CH_2Ph), 4.92–5.05 (m, 2H, 6-H), 5.82 (tdd, 1H, *J*=6.6, 10.1, 16.8 Hz, 5-H), 7.30–7.55 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): 14.1 (CH_3, 5′-C), 22.7, 24.9, 25.3, 32.1, 33.3, 33.8, 34.0 (all CH_2, 1′-C, 2-C, 2′-C, 3-C, 3′-C, 4-C, 4′-C), 51.1 (CH_2, CH_2Ph), 56.6 (CH, 1-C), 114.4 (CH_2, 6-C), 126.8, 128.2, 128.3 (all CH, all *C*H-Ph), 138.9 (CH, 5-C), 140.7 (C, C_q-Ph). $C_{18}H_{29}N$ (259.43): calcd C 83.33, H 11.27, N 5.40; found: C 83.18, H 11.26, N 5.56%.

*4.1.6. (+)-Calvine (**1**) and (+)-2-epicalvine (**2**).* $PdCl_2$ (83 mg, 0.469 mmol, 0,1 equiv), $CuCl_2$ (130 mg, 0.938 mmol, 0.2 equiv) and activated 3 Å molecular sieves (1 g) were placed in a dry, argon filled flask containing stirring bar and equipped with side-arm stopcock. Balloon with CO/O_2 mixture (ca. 1:1) was attached and the gases were exchanged by repeated evacuation (20 Torr) and filling (three times). Solids were left to stand as such for 20 min and then anhydrous dioxane (80 mL) was added. The brown suspension was stirred under CO/O_2 atmosphere for 1 h at 25 °C. The solution of aminoalkenitol **5** (1 g, 4.69 mmol) in anhydrous dioxane (14 mL) was then added and the resulting deep-green reaction mixture was stirred under CO/O_2 balloon for 45 h at 50 °C. After evaporation of volatiles in vacuo, ethyl acetate (150 mL) was added and the mixture was washed with 3% aq NH_4OH solution (150 mL). The water layer was extracted with ethyl acetate (3×100 mL), combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The resulting oil (1.299 g) was subjected to FLC (52 g SiO_2, 4×10 cm, ethyl acetate/hexanes/

triethylamine=14/86/1) yielding (+)-calvine **1** (177 mg, 16%) as colourless foam and (+)-2-epicalvine **2** (412 mg, 37%) as a pale-yellow oil. (+)-Calvine **1** was subsequently crystallised from heptane to obtain single-crystal suitable for X-ray analysis.

Compound **1**: mp=59 °C; $[\alpha]_D^{15}$ +16.6 (*c* 0.451, CH_2Cl_2) {Ref. 6 $[\alpha]_D^{20}$ +18 (*c* 0.66, CH_2Cl_2), Ref. 7 $[\alpha]_D^{20}$ +18.3 (*c* 0.35, CH_2Cl_2)}. All physico-chemical data were in perfect accordance with those previously published, see Ref. 6,7.

Compound **2**: $[\alpha]_D^{15}$ +8.7 (*c* 0.584, CH_2Cl_2) {Ref. 6 $[\alpha]_D^{20}$ +8 (*c* 0.58, CH_2Cl_2)}. All physico-chemical data were in perfect accordance with those previously published, see Ref. 6.

*4.1.7. (2S,6S)-(6-Pentylpiperidin-2-yl)acetic acid methyl ester (**3**) and (2R,6S)-(6-pentylpiperidin-2-yl)acetic acid methyl ester (**4**).* $PdCl_2$ (68 mg, 0.385 mmol, 0,1 equiv), $CuCl_2$ (104 mg, 0.77 mmol, 0.2 equiv) and activated 3 Å molecular sieves (1.04 g) were placed in a dry, argon filled flask containing stirring bar and equipped with side-arm stopcock. Balloon with CO/O_2 mixture (ca. 1:1) was attached and the gases were exchanged by repeated evacuation (20 Torr) and filling (three times). Solids were stirred for 10 min and then anhydrous MeOH (30 mL) was added. The deep-brown suspension was stirred under CO/O_2 atmosphere for 15 min at 25 °C. The solution of aminoalkene **6** (1 g, 3.85 mmol) in anhydrous MeOH (10 mL) was then added and the resulting brown-black reaction mixture was stirred under CO/O_2 balloon for 20 h at 28 °C. The mixture was diluted with CH_2Cl_2 (5 mL), filtered through Celite pad and rinsed with CH_2Cl_2 (2×15 mL). The residue after evaporation (1.362 g) was redissolved in ethyl acetate (100 mL), washed with 2% aq NH_4OH solution (2×70 mL) and brine (50 mL). The water phase was extracted with ethyl acetate (100 mL). Combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The resulting oil (1.225 g) was subjected to FLC (30 g SiO_2, 4×7 cm, diethylether/hexanes=4/1) yielding the mixture of metylesters **15**/**16** (827 mg, 68%) as a pale-yellow oil. This was dissolved in MeOH (45 mL) and $Pd(OH)_2$ (73 mg, 0.521 mmol, 0.2 equiv) was added. The resulting suspension was stirred under H_2 atmosphere (balloon) for 24 h at 25 °C. The reaction mixture was filtered through Celite pad and rinsed with CH_2Cl_2 (3×10 mL). The residue after evaporation (632 mg) was subjected to FLC (38 g SiO_2, 4×8 cm, 2-propanol/chloroform=1/25 containing 1% aq NH_4OH) yielding **3** (127 mg, 21%) and **4** (350 mg, 60%) as pale-yellow oils.

Compound **3**: R_f=0.8 (2-propanol/chloroform=1/25 containing 1% aq NH_4OH); $[\alpha]_D^{15}$ +22 (*c* 0.45, CH_2Cl_2) {Ref. 6 $[\alpha]_D^{20}$ +23 (*c* 0.52, $CHCl_3$)}.

Compound **4**: R_f=0.63 (2-propanol/chloroform=1/25 containing 1% aq NH_4OH); $[\alpha]_D^{15}$ +5.5 (*c* 0.58, $CHCl_3$) {Ref. 6 $[\alpha]_D^{20}$ +5 (*c* 0.53, $CHCl_3$)}. All physico-chemical data were in perfect accordance with those previously published, see Ref. 6.

Acknowledgements

We are very grateful to Prof. Tibor Gracza and Prof. František Považanec for their support and helpful discussions. We thank Dr. Naďa Prónayová for NMR service and Dr. Peter Zálupský for manuscript proof-reading. This work was supported by the Slovak Research and Development Agency under the contract No. APVV-0164–07. We also appreciate the financial support from EU Structural Funds, Interreg IIIA in purchasing the diffractometer.

Supplementary data

^1H and ^{13}C NMR spectra of **5**-**7**, **12**–**14**; X-ray structure refinement details of **1**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.01.106.

References and notes

1. Eisner, T.; Eisner, M.; Siegler, T. *Secret Weapons*; Harvard University: Harvard, 2007; pp. 59–337.
2. (a) Happ, G. M.; Eisner, T. *Science* **1961**, *134*, 329–331; (b) Pasteels, J. M.; Deroe, C.; Tursch, B.; Braekman, J.-C.; Daloze, D.; Hootele, C. *J. Insect Physiol.* **1973**, *19*, 1771–1784.
3. (a) Daloze, D.; Braekman, J.-C.; Pasteels, J. M. *Chemoecology* **1994**, *5*, 173–183; (b) King, G. A.; Meinwald, J. *Chem. Rev.* **1996**, *96*, 1105–1122; (c) Laurent, P.; Braekman, J.-C.; Daloze, D.; Pasteels, J. *Eur. J. Org. Chem.* **2003**, 2733–2743.
4. Strunz, G. M.; Findlay, J. A., Chapter 3 In *Pyridine and Piperidine Alkaloids in Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Elsevier: 1985; Vol. 26, pp. 89–183.
5. Braekman, J.-C.; Charlier, A.; Daloze, D.; Heilporn, S.; Pasteels, J.; Plasman, V.; Wang, S. *Eur. J. Org. Chem.* **1999**, 1749–1755.
6. Laurent, P.; Braekman, J.-C.; Daloze, D. *Eur. J. Org. Chem.* **2000**, 2057–2062.
7. Dewi-Wülfling, P.; Gebauer, J.; Blechert, S. *Synlett* **2006**, 487–489.
8. (a) Rougnon-Glasson, S.; Tratrat, C.; Canet, J.-L.; Chalard, P.; Troin, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 1561–1567; (b) Calvet-Vitale, S.; Vanucci-Bacqué, C.; Fargeau-Bellassoued, M.-C.; Lhommet, G. *Tetrahedron* **2005**, *61*, 7774–7782.
9. Szolcsányi, P.; Gracza, T.; Špánik, I. *Tetrahedron Lett.* **2008**, *49*, 1357–1360.
10. Nakayama, Y.; Kumar, G. B.; Kobayashi, Y. *J. Org. Chem.* **2000**, *65*, 707–715.
11. (a) Chattopadhyay, S.; Mamdapur, V. R.; Chadha, M. S. *Bull. Soc. Chim. Fr.* **1990**, 108–111; (b) Matsumoto, K.; Tsutsumi, S.; Ihori, T.; Ohta, H. *J. Am. Chem. Soc.* **1990**, *112*, 9614–9619; (c) Chow, S.; Kitching, W. *Tetrahedron: Asymmetry* **2002**, *13*, 779–794; (d) Tremblay, A. E.; Whittle, E.; Buist, P. H.; Shanklin, J. *Org. Biomol. Chem.* **2007**, *5*, 1270–1275.
12. For the alternative formation of the undesired bromohydrine **10** via opening the epoxide **9** with MgX_2, see: (a) Eisch, J. J.; Liu, Z.-R.; Ma, X.; Zheng, G.-X. *J. Org. Chem.* **1992**, *57*, 5140–5144; (b) Wang, T.; Ji, W.-H.; Xu, Z.-Y.; Zeng, B.-B. *Synlett* **2009**, 1511–1513.
13. The preparation of (*R*)-enantiomer of **13** is reported, however, no analytical data are available: (a) Takahata, H.; Yotsui, Y.; Momose, T. *Tetrahedron* **1998**, *54*, 13505–13516; (b) Shimizu, M.; Nemoto, H.; Kakuda, H.; Takahata, H. *Heterocycles* **2003**, *59*, 245–256.
14. (*S*)-enantiomer of **7** is known: (a) Fürstner, A.; Müller, T. *J. Org. Chem.* **1998**, *63*, 424–425; (b) Fürstner, A.; Müller, T. *J. Am. Chem. Soc.* **1999**, *121*, 7814–7821.
15. It is noteworthy that while the analytically pure racemic amino alcohol is an oil (see Ref. 9), (*R*)-enantiomer of **5** is a crystalline compound.
16. The extensive reaction screening was done earlier on a racemic substrate, see Ref. 9.
17. (a) Tamaru, Y.; Kobayashi, T.; Kawamura, S.-I.; Ochiai, H.; Yoshida, Z.-I. *Tetrahedron Lett.* **1985**, *26*, 4479–4482; (b) Tamaru, Y.; Hojo, M.; Yoshida, Z.-I. *J. Org. Chem.* **1988**, *53*, 5731–5741; (c) Jäger, V.; HÜmmer, W. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1171–1173; (d) Hümmer, W.; Dubois, E.; Gracza, T.; Jäger, V. *Synthesis* **1997**, 634–642; (e) Tamaru, Y.; Kimura, M. *Synlett* **1997**, 749–757; (f) Szolcsányi, P.; Gracza, T.; Koman, M.; Prónayová, N.; Liptaj, T. *Chem. Commun.* **2000**, 471–472; (g) Szolcsányi, P.; Gracza, T.; Koman, M.; Prónayová, N.; Liptaj, T. *Tetrahedron: Asymmetry* **2000**, *11*, 2579–2597.
18. (a) Fenton, D. M.; Steinwand, P. J. *J. Org. Chem.* **1974**, *39*, 701–704; (b) Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318–2323; (c) Karandin, A.; Gusevskaya, E. V.; Likhobolov, V. A.; Stepanov, A. G.; Talzi, E. P. *Kinet. Catal.* **1990**, *31*, 506–510; (d) Zargarian, D.; Alper, H. *Organometallics* **1991**, *10*, 2914–2921; (e) Hosokawa, T.; Nomura, T.; Murahashi, S.-I. *J. Organomet. Chem.* **1998**, *551*, 387–389; (f) Kawamura, Y.; Kawano, Y.; Matsuda, T.; Ishitobi, Y.; Hosokawa, T. *J. Org. Chem.* **2009**, *74*, 3048–3053.
19. All previous reports on the total synthesis of (+)-calvine 1 (see Ref. 6,7) describe the compound as an oil.
20. For X-ray measurement details and structure determination of **1** see Supplementary data. Crystallographic data (excluding structure factors) for the structure(s) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-730656. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK fax: (internet.)+441 223/336-033; e-mail: deposit@ccdc.cam.ac.uk.
21. Gallagher, A.; Davies, I. W.; Jones, S. W.; Lathbury, D.; Mathon, H. F.; Molloy, K. C.; Shaw, R. W.; Vernon, P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 433–440.
22. (a) Adams, D. R.; Carruthers, W.; Crowley, P. J. *J. Chem. Soc., Chem. Commun.* **1991**, 1261–1263; (b) Banwell, M. G.; Bui, C. T.; Pham, H. T. T.; Simpson, G. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 967–969; (c) Banwell, M. G.; Bissett, B. D.; Bui, C. T.; Pham, H. T. T.; Simpson, G. W. *Aust. J. Chem.* **1998**, *51*, 9–18; (d) Lee, E.; Jeong, E. J.; Min, S. J.; Hong, S.; Lim, J.; Kim, S. K.; Kim, H. J.; Choi, B. G.; Koo, K. C. *Org. Lett.* **2000**, *2*, 2169–2172; (e) Bargiggia, F. C.; Murray, W. V. *Tetrahedron Lett.* **2006**, *47*, 3191–3193.
23. K. Csatayová, PhD. Thesis, Slovak University of Technology, Bratislava, 2009.
24. The diastereomeric ratio of **3**/**4** was determined by the integration of MeO-signals (**3**: δ=3.66 ppm, **4**: δ=3.67 ppm) in the ^1H NMR spectrum of crude reaction mixture. The 2,6-*cis*-relative configuration of **3** was established by NOESY experiment. There is a through space interaction between 2-H (δ=2.94 ppm) and 6-H (δ=2.50 ppm).