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Tetrahedron Letters 49 (2008) 1357–1360
Tetrahedron Letters

Short racemic syntheses of calvine and epicalvine

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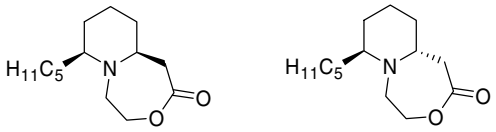
Received 15 October 2007; revised 12 December 2007; accepted 18 December 2007
Available online 14 January 2008

Abstract

The intramolecular Pd(II)-catalysed carbonylation of aminoalkenitol was used as a key step in the short racemic syntheses of the ladybird beetle alkaloids calvine and epicalvine. The title compounds have been prepared in 26% overall yield over four steps starting from hexanal and pentenyl bromide.

(+)-Calvine **1** and (+)-2-epicalvine **2** are bicyclic piperidine alkaloids found[1] in the haemolymph of the ladybird beetles *Calvia 10-guttata* and *Calvia 14-guttata* (Coccinellidae) (Fig. 1).

When molested or disturbed, beetles release small droplets of yellow 'blood' containing a toxic chemical cocktail at their knee joints (*reflex bleeding*).[2] As these insects are rarely eaten by predators, it is thought that both alkaloids function as efficient repellents.[3]

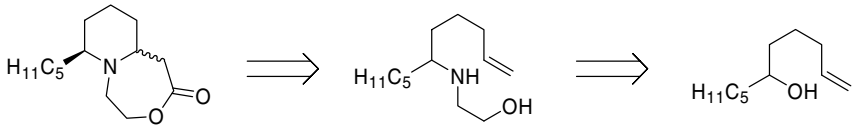


(+)-calvine (+)-2-epicalvine

Fig. 1. Alkaloids isolated from ladybird beetles.

The relative configuration of (+)-calvine **1** and (+)-2-epicalvine **2** was established on the basis of NMR and HRMS studies, and subsequently confirmed via racemic total synthesis.[1] The absolute configuration of both lactones was determined by enantioselective total syntheses,[4] since only one other preparation of **1** has appeared[5] along with two formal syntheses.[6,7]

Herein, we report a short racemic syntheses of the alkaloids calvine *rac*-**1** and epicalvine *rac*-**2** featuring Pd(II)-catalysed aminocyclisation–lactonisation[8] as a key step. Our retrosynthetic analysis led to the aminoalkenitol **3** as the key substrate, which is easily accessible from secondary alcohol **4** (Scheme 1).



rac-**1** (*cis*)
rac-**2** (*trans*) **3** **4**

Scheme 1. Retrosynthetic analysis of *rac*-**1** and *rac*-**2**.

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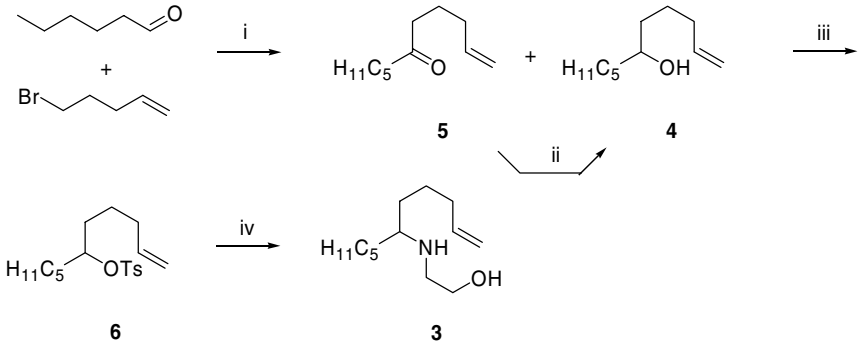
doi:10.1016/j.tetlet.2007.12.099

The total synthesis of *rac*-**1** and *rac*-**2** started with the Grignard addition of pentenylmagnesium bromide to hexanal, furnishing undec-1-en-6-ol[9] **4** in 67% yield along with undesired undec-1-en-6-one **5**[10] (16%). Reduction of **5** with $NaBH_4$ provided the desired alcohol **4** in 77% yield, leading to a combined overall yield of 80%. Activation of the hydroxyl group of **4** using TsCl gave tosylate[11] **6** in 79% yield. Finally, the treatment of **6** with excess ethanolamine gave the desired aminoalkenitol[12] **3** in 47% total yield over three steps[13] (Scheme 2).

With substrate **3** in hand, we subjected it to the final key transformation. The Pd(II)-catalysed aminocyclisation–lactonisation[14] was performed under various catalytic conditions in different solvents (Table 1). In all cases, we obtained a diastereomeric mixture of the desired alkaloids *rac*-**1** and *rac*-**2**, often accompanied by oxazolidinone **7** as a side-product.[15] After some experimentation, we identified the optimal catalytic system consisting of $PdCl_2$ as catalyst, excess $CuCl_2$ and AcONa as reoxidant and base, respectively (entry 3). These reaction conditions which involved heating in dioxane under a CO atmosphere afforded racemic calvine *rac*-**1** and epicalvine *rac*-**2** in 55% combined yield and in the ratio 2.2:1 along with traces of **7** (Scheme 3). If necessary, the undesired oxazolidinone **7** could be converted back to aminoalkenitol **3** under basic conditions[16] to recycle the starting material.

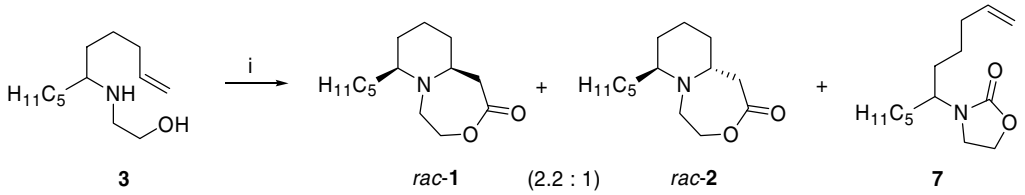


Scheme 2. Preparation of substrate **3**. Reagents and conditions: (i) Mg, Et_2O, rt–reflux, 2 h, **5** (16%) + **4** (67%); (ii) $NaBH_4$, MeOH, 0 °C, 30 min, 77%; (iii) 2 equiv TsCl, 19 equiv pyridine, CH_2Cl_2, 0 °C to rt, 18 h, 79%; (iv) 15 equiv $H_2N(CH_2)_2OH$, THF, reflux, 48 h, 75%.

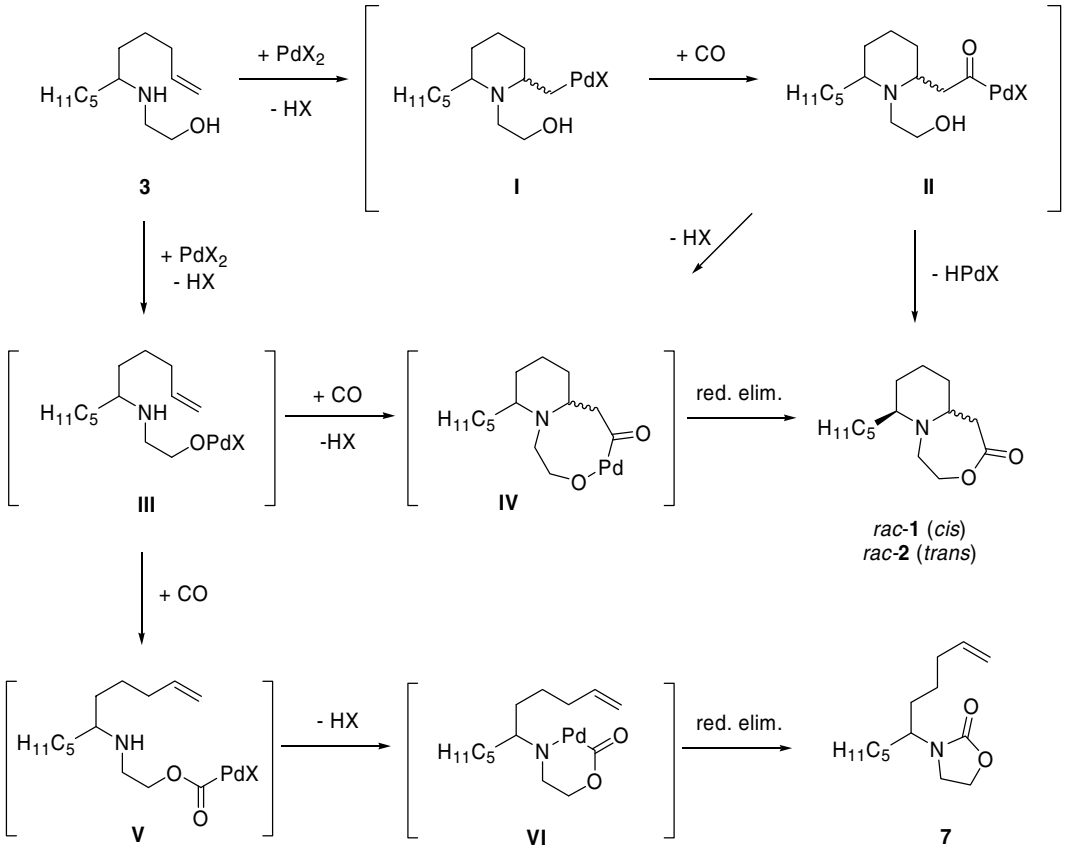
Table 1
Pd(II)-catalysed aminocyclisation–lactonisation of **3**

Entry	Pd-salt (0.1 equiv)	Reoxidant (2 equiv)	Base (2 equiv)	Solvent	Conditions	*rac*-**1**/*rac*-**2**/**7**[c]
1[a,b]	$PdCl_2$	$CuCl_2$	AcONa	AcOH	50 °C, 72 h	1.4/1.0/0
2[b]	$PdCl_2$	$CuCl_2$	AcONa	Et_2O	40 °C, 24 h	1.1/1.0/0
3	$PdCl_2$	$CuCl_2$	AcONa	Dioxane	40 °C, 7 h	9.0/4.0/1.0
4	$PdCl_2(MeCN)_2$	$CuCl_2$	AcONa	MeCN	26 °C, 24 h	2.4/1.0/1.2
5	$Pd(OAc)_2$	$CuCl_2$	AcONa	THF	28 °C, 24 h	1.8/1.0/3.6
6	$Pd(TFA)_2$	$CuCl_2$	AcONa	THF	28 °C, 22 h	1.8/1.0/2.4
7[b]	$Pd(OAc)_2$	$Cu(OAc)_2$	AcONa	THF	50 °C, 72 h	1.0/1.6/0
8	$PdCl_2$	$CuBr_2$	AcONa	THF	29 °C, 21 h	1.0/1.1/1.9
9	$PdCl_2$	$CuCl_2$	K_2CO_3	Dioxane	30 °C, 5 h	16.0/16.3/1.0
10	$Pd(OAc)_2$	$CuCl_2$	Et_3N	Dioxane	40 °C, 24 h	2.6/1.0/1.8
11[d]	$Pd(OAc)_2$	O_2	None	Dioxane	50 °C, 24 h	6.0/5.0/1.0
12	$Pd(OAc)_2$	$CuCl_2$	Et_3N	Toluene	33 °C, 20 h	1.5/1.0/2.1
13	$Pd(OAc)_2$	$CuCl_2$	None	Toluene	40 °C, 24 h	2.3/2.0/1.0

[a] Three equivalents of reoxidant and base were used.
[b] Complex mixture.
[c] Relative ratios were determined by the GC analyses of crude reaction mixtures.
[d] Molecular sieves (3 Å) were added.



Scheme 3. Pd(II)-catalysed aminocyclisation–lactonisation of **3**. Reagents and conditions: (i) CO (balloon), 0.1 equiv $PdCl_2$, 2 equiv $CuCl_2$, 2 equiv AcONa, dioxane, 40 °C, 7 h, *rac*-**1** + *rac*-**2** (55%, 2.2:1), **7** (4%).



Scheme 4. Proposed mechanisms for the Pd(II)-catalysed aminocyclisation–lactonisation of **3** and formation of products *rac*-**1**, *rac*-**2** and **7**.

Mechanistically, the intramolecular aminocarbonylation of **3** proceeds most likely via an initially formed σ-palladium complex **I** that quickly accepts carbon monoxide to produce the corresponding σ-acylpalladium complex **II**. This intermediate finally undergoes reductive elimination to furnish products *rac*-**1** and *rac*-**2**. Alternatively, the formation of palladium alkoxide **III** cannot be excluded, which after CO insertion and intramolecular nucleophilic addition (or vice versa) may form the bicyclic intermediate **IV**. The final reductive elimination would again lead to the observed products *rac*-**1** and *rac*-**2**. The formation of undesired oxazolidinone **7** can result from alkoxide **III**. Once formed, **III** may intercept CO to generate an acyclic σ-acylpalladium complex **V**. If this is the case, the reductive elimination via **VI** occurs much more quickly than bicyclisation finally leading to undesired oxazolidinone **7** (Scheme 4).

In conclusion, we have used a Pd(II)-catalysed aminocyclisation–lactonisation of **3** as a key step in the short racemic total synthesis of the alkaloids calvine *rac*-**1** and epicalvine *rac*-**2**. The title compounds were obtained in 26% overall yield over four steps.

Acknowledgements

We thank Professor František Považanec for helpful discussions. We are grateful to Mrs. Mária Krajčírová for technical assistance, to Dr. Naďa Prónayová for NMR service and to Dr. Peter Zálupský for performing the preliminary quantum-chemical calculations as well as the manuscript proofreading. This work was supported by Science and Technology Assistance Agency under the Contract No. APVT-20-000904 and Slovak National R&D Programme No. 2003SP200280203.

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11. Selected data for toluene-4-sulfonic acid 1-pentyl-hex-5-enyl ester **6**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.82$ (t, 3H, CH_3), 1.19–1.44 (m, 8H, H-3, H-2′, H-3′, H-4′), 1.50–1.67 (m, 4H, H-2, H-1′), 1.90–2.00 (m, 2H, H-4), 2.44 (s, 3H, CH_3Ph), 4.54 (m, 1H, H-1), 4.88–4.98 (m, 2H, H-6), 5.69 (ddt, 1H, H-5), 7.32 (d, 2H, $J = 8.1$ Hz, CH_m-Ph), 7.79 (d, 2H, $J = 8.1$ Hz, CH_o-Ph). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.9$ (q, CH_3), 21.6 (q, CH_3Ph), 22.4, 23.8, 24.3, 31.4 (4 × *t*, C-3, C-2′, C-3′, C-4′), 33.2, 33.5, 34.0 (3 × *t*, C-2, C-4, C-1′), 84.3 (d, C-1), 114.8 (t, C-6), 127.7 (d, CH_o-Ph), 129.6 (d, CH_m-Ph), 134.6 (s, CH_3C), 138.1 (d, C-5), 144.3 (s, CSO_2). IR (KBr, ν/cm^{-1}): 666, 815, 905, 1097, 1176, 1188, 1362, 2862, 2932, 2954.
12. Selected data for 2-(1-pentyl-hex-5-enylamino)-ethanol **3**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.87$ (t, 3H, CH_3), 1.20–1.45 (m, 12H, H-2, H-3, H-1′, H-2′, H-3′, H-4′), 1.95–2.15 (m, 2H, H-4), 2.43 (br s, 2H, exchange with D_2O, NH, OH), 2.45–2.55 (m, 1H, H-1), 2.74 (t, 2H, CH_2NH), 3.60 (t, 2H, CH_2OH), 4.90–5.02 (m, 2H, H-6), 5.79 (ddt, 1H, H-5). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.0$ (q, CH_3), 22.6, 24.9, 25.3, 32.1, 33.4, 33.9, 33.9 (7 × *t*, C-2, C-3, C-4, C-1′, C-2′, C-3′, C-4′), 48.0 (t, CH_2NH), 57.1 (d, C-1), 61.0 (t, CH_2OH), 114.5 (t, C-6), 138.7 (d, C-5). IR (KBr, ν/cm^{-1}): 910, 1062, 1459, 1641, 2858, 2929, 3077, 3313.
13. An identical sequence on analogous compounds is reported, see: Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792–803.
14. Typical procedure for the intramolecular Pd(II)-catalysed carbonylation: A mixture of aminoalkenitol **3** (100 mg, 0.469 mmol), $PdCl_2$ (8 mg, 0.045 mmol, 0.1 equiv), $CuCl_2$ (126 mg, 0.937 mmol, 2 equiv) and AcONa (77 mg, 0.937 mmol, 2 equiv) in dry dioxane (9 mL) was stirred under a CO atmosphere (balloon) at 40 °C for 7 h. The resulting suspension was filtered, the solids were washed with Et_2O (10 mL) and the filtrate was evaporated. The green residue was suspended in Et_2O (20 mL) and washed with 5% aq NH_4OH (2 × 10 mL). The combined washings were back-extracted with Et_2O (20 mL) and the combined organic extracts were washed with H_2O (10 mL), dried over $MgSO_4$ and evaporated to furnish a red-brown oil (96 mg). Flash chromatography purification (SiO_2, hexanes/AcOEt/Et_3N = 86/14/1) yielded three fractions: oxazolidinone **7** as a yellowish oil (5 mg, 4%), calvine *rac*-**1** as a yellowish oil (45 mg, 38%) and epicalvine *rac*-**2** as a yellowish oil (20 mg, 17%).
15. Selected data for 3-(1-pentyl-hex-5-enyl)-oxazolidin-2-one **7**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.86$ (t, 3H, $J = 6.8$ Hz, CH_3), 1.20–1.88 (m, 12H, 7 × CH_2), 1.94–2.16 (m, 2H, CH_2CH=CH_2), 3.39 (t, 2H, $J = 8.1$ Hz, CH_2N), 3.70–3.86 (m, 1H, CHN), 4.31 (t, 2H, $J = 8.1$ Hz, CH_2O), 4.92–5.02 (m, 2H, H-6), 5.76 (ddt, 1H, H-5). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.0$ (q, CH_3), 22.6, 25.4, 25.9, 31.6, 31.8, 32.5, 33.4 (7 × *t*, 7 × CH_2), 39.5 (t, CH_2N), 53.2 (d, CH), 61.9 (t, CH_2O), 115.0 (t, CH_2=CH), 138.3 (d, CH_2 = CH), 158.5 (s, C=O). Anal. Calcd for $C_{14}H_{25}NO_2$ (239.21): C, 70.25; H, 10.53; N, 5.85%. Found: C, 70.20; H, 10.58; N, 5.88%. Preparation of N-substituted oxazolidinones via Pd(II)-catalysed carbonylation of 1,2-amino-alcohols is known: Tam, W. *J. Org. Chem.* **1986**, *51*, 2977–2981; Chiarotto, I.; Feroci, M. *Tetrahedron Lett.* **2001**, *42*, 3451–3453.
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