

Short racemic syntheses of calvine and epicalvine

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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.

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(+)-Calvine **1** and (+)-2-epicalvine **2** are bicyclic piperidine alkaloids found¹ 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

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 appeared⁵ 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–lactonisation⁸ 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).

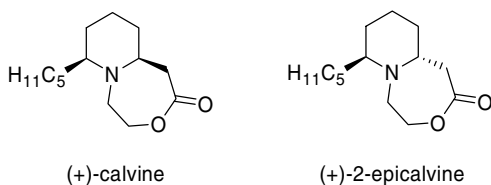
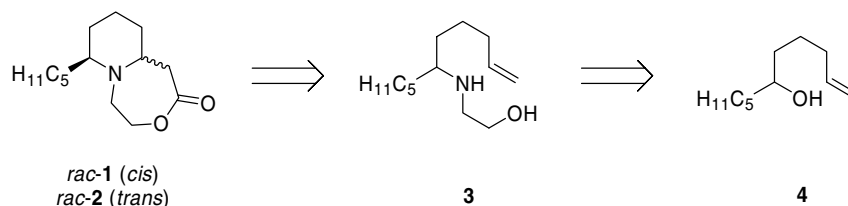


Fig. 1. Alkaloids isolated from ladybird beetles.



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

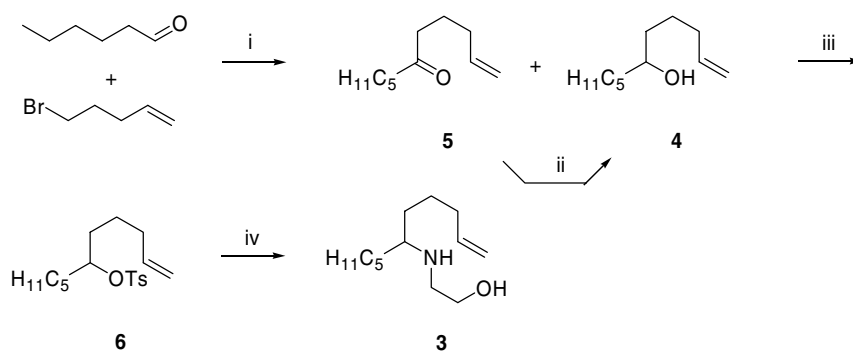
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The total synthesis of *rac-1* and *rac-2* started with the Grignard addition of pentenylmagnesium bromide to hexanal, furnishing undec-1-en-6-ol⁹ **4** in 67% yield along with undesired undec-1-en-6-one **5**¹⁰ (16%). Reduction of **5** with NaBH₄ 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 tosylate¹¹ **6** in 79% yield. Finally, the treatment of **6** with excess ethanolamine gave the desired aminoalkenitol¹² **3** in 47% total yield over three steps¹³ (Scheme 2).

With substrate **3** in hand, we subjected it to the final key transformation. The Pd(II)-catalysed aminocyclisation–lactonisation¹⁴ 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 PdCl₂ as catalyst, excess CuCl₂ 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 conditions¹⁶ to recycle the starting material.



Scheme 2. Preparation of substrate **3**. Reagents and conditions: (i) Mg, Et₂O, rt–reflux, 2 h, **5** (16%) + **4** (67%); (ii) NaBH₄, MeOH, 0 °C, 30 min, 77%; (iii) 2 equiv TsCl, 19 equiv pyridine, CH₂Cl₂, 0 °C to rt, 18 h, 79%; (iv) 15 equiv H₂N(CH₂)₂OH, THF, reflux, 48 h, 75%.

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

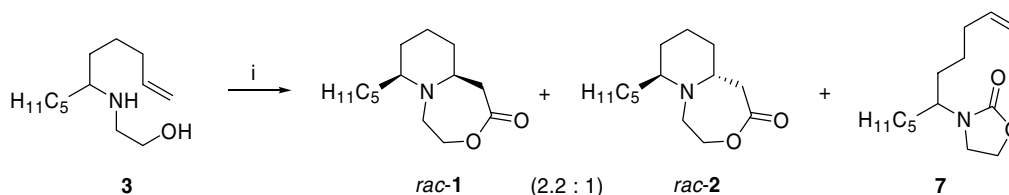
Entry	Pd-salt (0.1 equiv)	Reoxidant (2 equiv)	Base (2 equiv)	Solvent	Conditions	<i>rac-1</i> / <i>rac-2</i> / 7 ^c
1 ^{a,b}	PdCl ₂	CuCl ₂	AcONa	AcOH	50 °C, 72 h	1.4/1.0/0
2 ^b	PdCl ₂	CuCl ₂	AcONa	Et ₂ O	40 °C, 24 h	1.1/1.0/0
3	PdCl ₂	CuCl ₂	AcONa	Dioxane	40 °C, 7 h	9.0/4.0/1.0
4	PdCl ₂ (MeCN) ₂	CuCl 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 ₂ CO ₃	Dioxane	30 °C, 5 h	16.0/16.3/1.0
10	Pd(OAc) ₂	CuCl ₂	Et ₃ N	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 ₃ N	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.

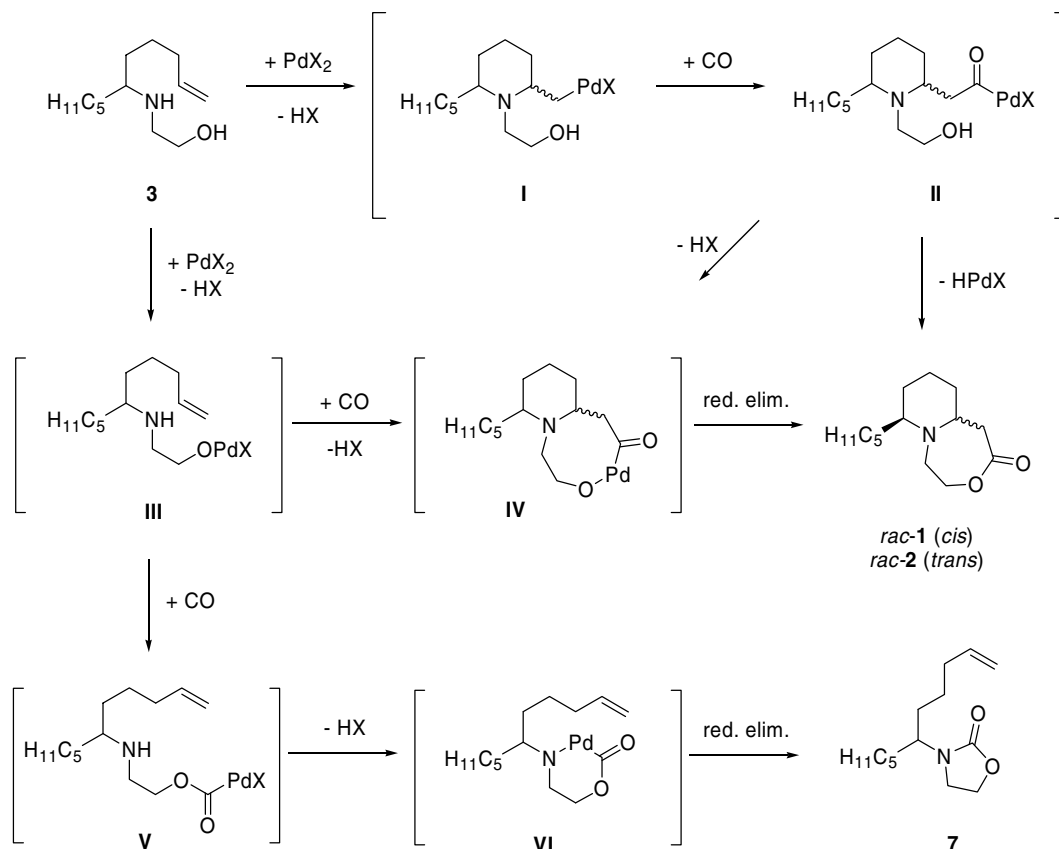
^b Complex mixture.

^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 PdCl₂, 2 equiv CuCl₂, 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.

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11. Selected data for toluene-4-sulfonic acid 1-pentyl-hex-5-enyl ester **6**: ^1H NMR (300 MHz, CDCl_3): δ = 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, $\text{CH}_m\text{-Ph}$), 7.79 (d, 2H, J = 8.1 Hz, $\text{CH}_o\text{-Ph}$). ^{13}C NMR (75 MHz, CDCl_3): δ = 13.9 (q, CH_3), 21.6 (q, CH_3Ph), 22.4, 23.8, 24.3, 31.4 (4 \times t, C-3, C-2', C-3', C-4'), 33.2, 33.5, 34.0 (3 \times t, C-2, C-4, C-1'), 84.3 (d, C-1), 114.8 (t, C-6), 127.7 (d, $\text{CH}_o\text{-Ph}$), 129.6 (d, $\text{CH}_m\text{-Ph}$), 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**: ^1H NMR (300 MHz, CDCl_3): δ = 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): δ = 14.0 (q, CH_3), 22.6, 24.9, 25.3, 32.1, 33.4, 33.9, 33.9 (7 \times 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 \times 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/ $\text{AcOEt}/\text{Et}_3\text{N}$ = 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**: ^1H NMR (300 MHz, CDCl_3): δ = 0.86 (t, 3H, J = 6.8 Hz, CH_3), 1.20–1.88 (m, 12H, 7 \times CH_2), 1.94–2.16 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$), 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): δ = 14.0 (q, CH_3), 22.6, 25.4, 25.9, 31.6, 31.8, 32.5, 33.4 (7 \times t, 7 \times CH_2), 39.5 (t, CH_2N), 53.2 (d, CH), 61.9 (t, CH_2O), 115.0 (t, $\text{CH}_2=\text{CH}$), 138.3 (d, $\text{CH}_2=\text{CH}$), 158.5 (s, $\text{C}=\text{O}$). Anal. Calcd for $\text{C}_{14}\text{H}_{25}\text{NO}_2$ (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-aminoalcohols 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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