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A Tandem Synthesis of (±)-Euphococcinine and (±)-Adaline

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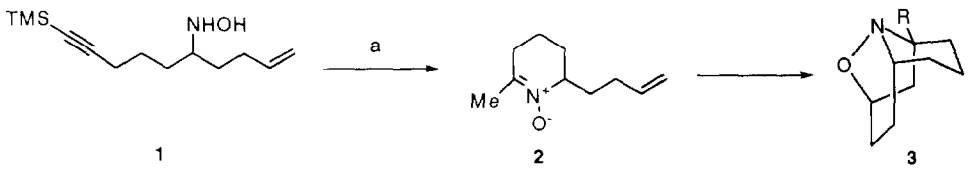
Abstract: Intramolecular hydroxylamine-alkyne cyclisation of the hydroxylamines **8** and **9** afforded six-membered cyclic nitrones which without isolation underwent a tandem intramolecular dipolar cycloaddition to produce the tricyclic isoxazolidines **6** and **7** respectively. These were converted in two steps into the ladybird defence alkaloids (±)-euphococcinine **4** and (±)-adaline **5**.

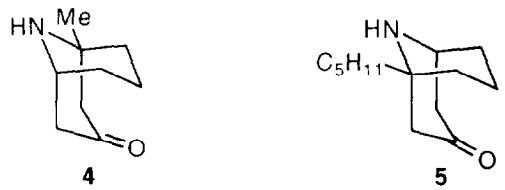
We have previously described the hydroxylamine-alkyne cyclisation of **1** to give the cyclic nitrone **2**, followed by tandem intramolecular dipolar cycloaddition to afford the tricyclic adduct **3** (R = Me) (Scheme1),[1] and we have explored the scope of this cyclisation as a general route to five-, six- and seven-membered cyclic nitrones.[2] In this Letter the tandem methodology is applied to a concise synthesis of the ladybird defence alkaloids adaline **4** and euphococcinine **5**.



1 2 3

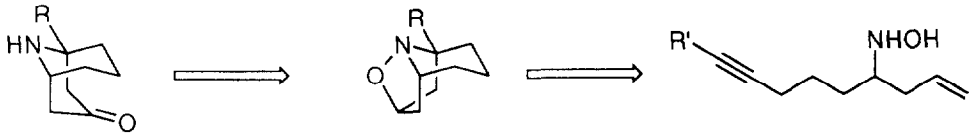
Scheme 1 *Reagents and conditions :* (a) Toluene, reflux, 14 h (83%)

Euphococcinine **4** was first isolated from a small sea-coast plant, *Euphorbia atoto* Forst.,[3] but has subsequently been found as part of the chemical defence system of both the Australian mealybug ladybird, *Cryptolaemus montrouzieri*,[4] and the Mexican bean beetle, *Epilachna varivestis*.[5] The enantiomerically related alkaloid, adaline **5**, also acts as part of the defence system of the European ladybird, *Adalia bipunctata*, and also has been isolated from *Quadrimaculata* Scopoli and *Pantherina L.*[6] Both alkaloids are proven feeding deterrents to spiders and ants.



4 5

A variety of approaches to these alkaloids have been described.[7,8] Both euphococcinine **4** and adaline **5** could be synthesised in racemic form *via* the tricyclic systems of the type **6** and **7**, which could be easily prepared from acyclic hydroxylamines such as **8** and **9** (Scheme 2).



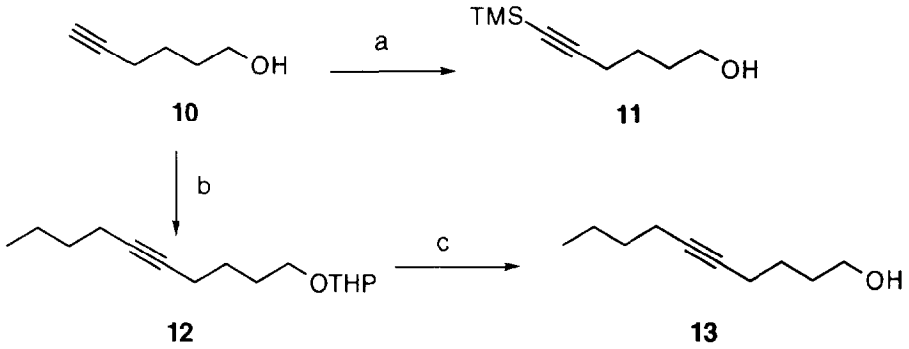
(±)-**4**; R = Me
(±)-**5**; R = C_5H_{11}

6; R = Me
7; R = C_5H_{11}

8; R' = TMS
9; R' = C_4H_9

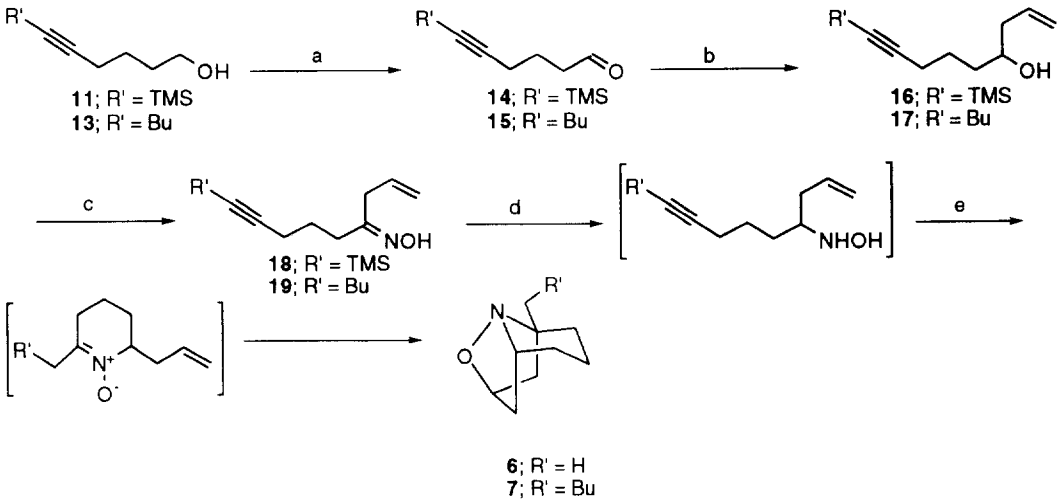
Scheme 2

5-Hexyn-1-ol **10** was chosen as the starting material for both the natural products. Silylation of the terminal alkyne and the primary alcohol, followed by cleavage of the trimethylsilyl ether gave the alcohol **11** for euphococcinine. Alternatively, formation of 1-tetrahydropyranyloxy-5-hexyne **12**, followed by alkylation using butyllithium, tetramethylethylenediamine (TMEDA) and iodobutane, and acetal cleavage afforded the alcohol **13** which served as the key starting compound for adaline.



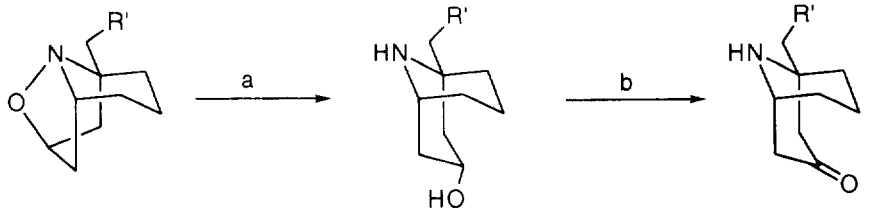
Scheme 3 *Reagents and conditions:* (a) (i) *n*BuLi, (ii) TMSCl, (iii) HCl aqueous (76%); (b) (i) Dihydropyran, Amberlyst-15 resin, (ii) *n*BuLi, TMEDA, followed by BuBr (60%); (c) Amberlyst-15, MeOH.

Swern oxidation[9] of the alcohols **11** and **13** gave the aldehydes **14** and **15** in good yield (Scheme 4). Addition of allyl magnesium bromide gave the secondary alcohols **16** and **17**. Oxidation of the alcohols using CrO_3-HOAc,[10] followed by treatment with hydroxylamine hydrochloride in pyridine-ethanol gave the oximes **18** and **19**. These were reduced to the corresponding hydroxylamines using sodium cyanoborohydride at pH 3-4. The hydroxylamines were heated to reflux in toluene for 9-12 hours. The resulting nitrones were not isolated, but underwent *in situ* intramolecular dipolar cycloaddition to afford the tricyclic adducts **6** and **7**.



Scheme 4 *Reagents and conditions :* (a) Oxalyl chloride, DMSO, Et_3N (80-90%); (b) CH_2=$CHCH_2MgBr$, ether (70-81%); (c) (i) CrO_3, HOAc, (ii) $NH_2OH.HCl$, Py-EtOH (58-66%); (d) $NaCNBH_3$, MeOH, pH 3-4; (e) Toluene, reflux, 9 h (71-76%).

The tricyclic systems were formed in good yield, allowing completion of the syntheses according to the route used by Gössinger[8] for adaline. Reductive cleavage of the N-O bond, using Raney-nickel and hydrogen, afforded the bicyclic alcohols **20** and **21** in excellent yield. Oxidation of the alcohols with pyridinium chlorochromate gave the required alkaloids (±)-euphococcinine **1** and (±)-adaline **2** respectively, in good yields (Scheme 5).[11]



Scheme 5 *Reagents and conditions*: (a) Raney-Ni, H_2, 90 min (93-96%); (b) PCC, CH_2Cl_2 (70-72%)

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11. All new compounds exhibited spectroscopic and microanalytical/high resolution mass spectral data in accord with the assigned structure.
    Selected spectroscopic data: Isoxazolidine **6**: δ_H (250 MHz, $CDCl_3$) 4.64 (1H, t, *J* 5 Hz), 3.50-3.39 (1H, m), 1.92-1.79 (1H, m), 1.70-1.50 (4H, m), 1.44-1.22 (5H, m), 1.05 (3H, s); δ_C (100 MHz, $CDCl_3$) 81.7 (d), 65.1 (s), 61.1 (d), 43.2 (t), 35.9 (t), 33.3 (t), 31.4 (q), 25.5 (t), 14.4 (t); *m/z* (EI) 153 (MH^+, 18%), 126 (30), 105 (29), 79 (76), 73 (74), 55 (100), 41 (98); [Found: M+H$^+$ 154.1232 (EI). $C_9H_{15}NO$ requires *M+H* 154.1232]; Euphococcinine **4**: δ_H (400 MHz, $CDCl_3$) 3.72-3.68 (1H, m), 2.58 (1H, dd, *J* 16, 6.6 Hz), 2.37 (1H, dd, *J* 16, 2.5 Hz), 2.33 (1H, d, *J* 16 Hz), 2.23 (1H, d, *J* 16Hz), 1.76-1.42 (7H, m), 1.19 (3H, s); δ_C (100 MHz, $CDCl_3$) 210.5 (s), 53.2 (t), 52.5 (s), 49.8 (d), 45.9 (t), 38.6 (t), 31.3 (q), 30.9 (q), 17.9 (t); *m/z* (EI) 153 (M^+, 9%), 110 (44), 96 (52), 82 (41), 55 (26), 42 (100), 39 (56); [Found : M^+ 153.1154 (EI). $C_9H_{15}NO$ requires M^+ 153.1154]; Isoxazolidine **7**: δ_H (250 MHz, $CDCl_3$) 4.74 (1H, t, *J* 5.3 Hz), 3.60-3.44 (1H, m), 2.00-1.70 (5H, m), 1.55-1.40 (5H, m), 1.30-1.15 (8H, m), 0.86 (3H, t, *J* 7.2 Hz); δ_C (100 MHz, $CDCl_3$) 81.5 (d), 68.0 (q), 61.2 (d), 43.2 (t), 41.7 (t), 36.3 (t), 32.5 (t), 30.1 (t), 25.4 (t), 23.1 (t), 22.7 (t), 14.2 (t), 14.2 (q); *m/z* (EI) 209 (M^+, 38 %), 180 (40), 168 (60), 153 (52), 112 (100); [Found : M^+ 209.1780 (EI). $C_{13}H_{23}NO$ requires M^+ 209.1780]; Adaline **5**: δ_H (400 MHz, $CDCl_3$) 3.68-3.64 (1H, m), 2.53 (1H, dd, *J* 16, 6.6 Hz), 2.37 (2H, 2 coincident d, *J* 16 Hz), 2.18 (1H, d, *J* 16 Hz), 1.74-1.60 (5H, m), 1.51-1.26 (10H, m), 0.88 (3H, t, *J* 6.6 Hz); δ_C (100 MHz, $CDCl_3$) 211.4 (s), 54.7 (s), 51.6 (t), 49.7 (d), 46.6 (t), 44.7 (t), 36.6 (t), 32.4 (t), 31.6 (t), 22.6 (t), 22.3 (t), 17.9 (t), 14.0 (q); *m/z* (EI) 209 (M^+, 50 %), 180 (22), 166 (86), 153 (100), 110 (68), 96 (78); [Found: M^+ 209.1779 (EI). $C_{13}H_{23}NO$ requires M^+ 209.1780)].

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