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A Simple Stereoselective synthesis of "Galbanolene", (3*E*, 5*Z*)-1,3,5-undecatriene

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Abstract: A new synthesis of (3*E*, 5*Z*)-1,3,5-undecatriene (**2**) is presented, based on a *Mannich* addition to 1,4 decadiyne, followed by *Lindlar* hydrogenation and *Hofmann* elimination. This "one pot" coupling of C_7+C_3+C_1 synthons affords **2** stereochemically pure.

Following their discovery in the essential oil of galbanum (*Ferula galbaniflua*) [1] and Hawaian seaweed (*Dictyopteris plagiogramma*) [2], the four stereoisomers of 1,3,5-undecatriene **2** were synthesised and submitted for olfactive evaluation [3].

The (3*Z*,5*Z*)-isomer is known to be unstable, readily isomerising to **3** by a 1,7 sigmatropic shift, while the (3*E*, 5*E*)-isomer possesses only a weak galbanum note. The most interesting galbanum fragrance is exhibited by the (3*E*, 5*Z*)-isomer **2**, motivating the publication of several non-stereoselective [4] and stereoselective syntheses [5–8].

Nevertheless, none of them has become eligible for a viable industrial process, due to economic reasons (price, availability of starting materials), ecological considerations, safety problems (allergenic and carcinogenic properties of the intermediates) or simple technical aspects such as prohibitive dilution conditions.

We therefore decided to design a synthesis based on the following prerequisites:

a) cheap, available and inoffensive starting materials
b) simple and classical industrial transformations
c) simple purification techniques.

In view of the crucial last step of the most recent stereoselective synthesis (scheme 1) [8i],

Scheme 1

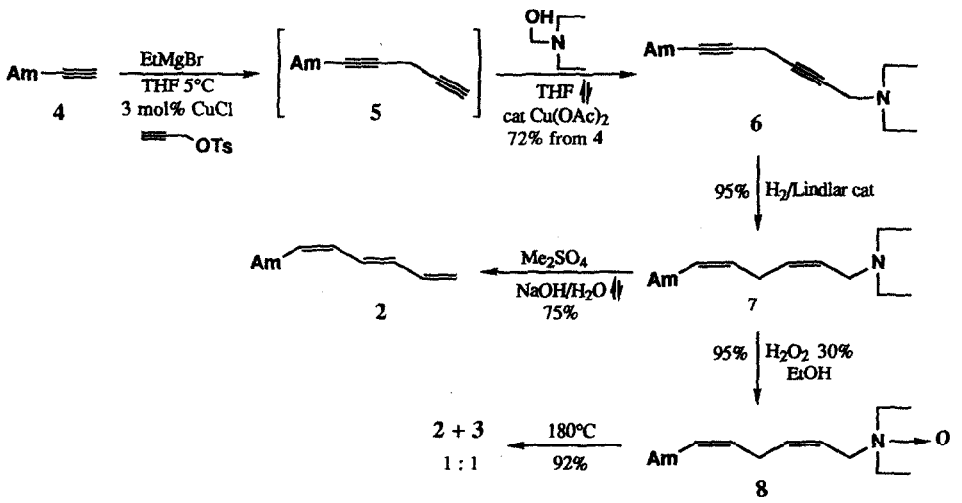
1 8 : 92 E : Z **2** 96 : 4 **3**

it was considered that a 2,5-diyne would be a precursor of choice to introduce the desired (2*Z*, 5*Z*)-stereochemistry in intermediate **1**.

Furthermore, employing an amine as leaving group would allow purification by simple extraction and avoid dermatological problems, due to possible traces of chlorinated compounds in the final product.

The following synthetic strategy was thus envisaged (*Scheme 2*).

Scheme 2



Refluxing the known crude 1,4-decadiyne (**5**) [9] in THF with *p*-formaldehyde and diethylamine in the presence of $Cu(OAc)_2 \cdot H_2O$ (1.5 mol%) gave the *Mannich* adduct, aminodiyne **6** in 72% overall yield from 1-heptyne (**4**) [10]. Subsequent hydrogenation over *Lindlar* catalyst (2.5% by weight) then afforded the stereoisomerically pure aminodiene **7** (95% yield). *Hofmann* elimination [11] using dimethyl sulfate in refluxing aqueous NaOH [12] yielded (75%) the single (3*E*, 5*Z*)-isomer **2**. The residual diethylmethyl amine was extracted with acetic or oxalic acid to pH > 6 to prevent the slight isomerisation of **2** observed at higher acidity. A possible alternative access, *via* pyrolysis of N-oxide **8** [13], unselectively furnished a 1:1 mixture of **2** and **3**.

Considering the efficiency of this linear, stereoselective synthesis ($C_7+C_3+C_1$ instead of C_7+C_4 synthons), it is noteworthy that the complete reaction sequence may be conducted in a "one pot" procedure. The intermediates are stable to distillation or acidic extraction [14]. This approach thus favorably compares with a recent expeditive synthesis [15] or with other modern triene syntheses [16].

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6 IR: 2950, 1460, 1380, 1310, 1200, 1090.
^1H-NMR: 0.90 (*t*, *J*=7, 3H); 1.06 (*t*, *J*=7, 6H); 1.35 (*m*, 4H); 1.50 (*m*, 2H); 2.15 (*tt*, J_1=7, J_2=2, 2H); 2.55 (*q*, *J*=7, 4H); 3.16 (*t*, *J*=2, 2H); 3.40 (*t*, *J*=2, 2H).
^{13}C-NMR: 9.7 (*t*), 12.6 (2*q*), 14.0 (*q*), 18.7 (*t*), 22.3 (*t*), 28.5 (*t*), 31.1 (*t*), 41.2 (*t*), 47.2 (2*t*), 74.2 (*s*), 75.0 (*s*), 79.3 (*s*), 80.7 (*s*).
MS: $M^{+\cdot}$ 219 (4), 204 (100), 91 (30), 58 (21).
Bp: 70°C/0.1 Torr.

7 IR: 2950, 1650, 1460, 1380, 1200, 1170, 1060, 790.
^1H-NMR: 0.90 (*t*, *J*=7, 3H); 1.05 (*t*, *J*=7, 6H); 1.30 (*m*, 6H); 2.05 (*q*, *J*=7, 2H); 2.53 (*q*, *J*=7, 4H); 2.82 (*t*, *J*=5, 2H); 3.15 (*d*, *J*=5, 2H); 5.37 (*m*; 2H); 5.50 (*t*, *J*=5, 2H)..
^{13}C-NMR: 11.9 (2*q*), 14.0 (*q*), 22.6 (*t*), 26.0 (*t*), 27.3 (*t*), 29.4 (*t*), 31.6 (*t*), 46.9 (2*t*), 49.8 (*t*), 127.3 (*d*), 127.5 (*d*), 130.6 (2*d*).
MS: $M^{+\cdot}$ 223 (3), 208 (4), 164 (5), 150 (30), 125 (27), 112 (100), 110 (77), 79 (86), 58 (75).
Bp: 60°C/0.02 Torr

8 IR: 2950, 1650, 1460, 1380, 790.
^1H-NMR: 0.90 (*t*, *J*=7, 3H); 1.30 (*m*, 6H); 1.37 (*t*, *J*=7, 6H); 2.04 (*q*, *J*=7, 2H); 2.87 (*t*, *J*=7, 2H); 3.32 (*q*, *J*=7, 4H); 3.95 (*d*, *J*=7, 2H); 5.28 (*m*, 1H); 5.46 (*m*, 1H); 5.75 (*m*, 1H); 5.83 (m, 1H).
^{13}C-NMR: 8.3 (2*q*), 14.0 (*q*), 22.6 (t), 26.4 (*t*), 27.4 (*q*), 29.2 (*t*), 31.5 (*t*), 59.6 (2*t*), 61.7 (t), 118.3 (*d*), 125.5 (*d*), 132.0 (*d*), 137.3 (*d*).
MS: $M^{+\cdot}$ 239 (1), 151 (8), 109 (18), 95 (39), 89 (92), 81 (50), 74 (100), 67 (67), 55 (49), 41 (36).

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