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Efficient Synthesis of (*S,Z*)-Dodec-3-en-11-olide (Ferrulactone II) using 2-Carboxyethyltriphenylphosphonium Bromide

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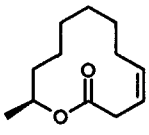
The aggregation pheromone component of rusty grain beetle *Cryptolestes ferrugineus*, ferrulactone II, has been synthesized based on Wittig reaction of the title phosphonium salt with (*S*)-8-(2-tetrahydropyranyl)oxynonanal readily available, in turn, from (*S*)-methyloxirane.

The 12-membered macrolide, ferrulactone II **1**, is one of the main pheromone components produced by the male of the rusty grain beetle *Cryptolestes ferrugineus* Stephen, a serious world-wide pest of stored food product.[1] This compound potentially can be used to increase the efficiency of detection traps for *C. ferrugineus*.



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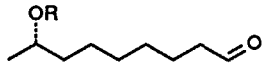
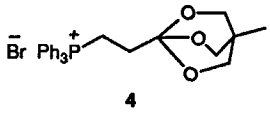


2 R = TBDMS
3 R = THP



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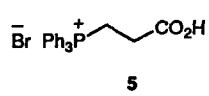


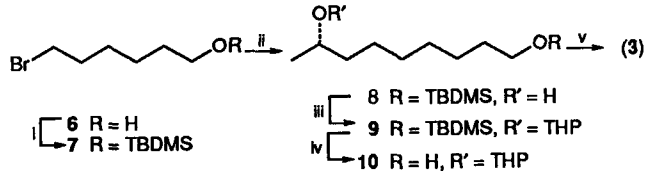
5

Five syntheses of **1** have been published so far. Four of them used appropriate acetylenic precursors for the creation of a (*Z*)-disubstituted double bond.[2,3] The fifth approach[4] is based on the Wittig reaction of aldehyde **2** with phosphonium salt **4** which represents a protected form of the carboxyphosphonium salt **5**. Here we describe a simple and efficient synthesis of pheromone **1** based on a readily available salt **5**[5] and chiral aldehyde **3**.

α,ω-Bromoalcohol **6** in the form of its *tert*-butyldimethylsilyl (TBDMS) ether **7**‡ served as the starting material for the synthesis of the aldehyde **3** (Scheme 1). Coupling of Grignard reagent, prepared from the bromide **7**, with (*S*)-methyloxirane in the presence of copper bromide–dimethyl sulfide complex furnished (*S*)-alcohol **8** in high yield. Preparation of tetrahydropyranyl (THP) derivative **9** followed by desilylation of this diether were performed conventionally to give the monoprotected diol **10** in 90% yield from **8**. Oxidation of **10** with pyridinium chlorochromate (PCC) afforded the desired aldehyde **3** which was further used without additional purification. The key step of the whole sequence consists of Wittig olefination of **3** with phosphorane generated from the phosphonium salt **5**.

† Professor Alexander Moiseenkov, Corresponding Member of the Russian Academy of Sciences, Renowned scientist and Butlerov Prize winner, died on the 1st November 1992.

‡ All new compounds gave satisfactory spectroscopic and analytical data.



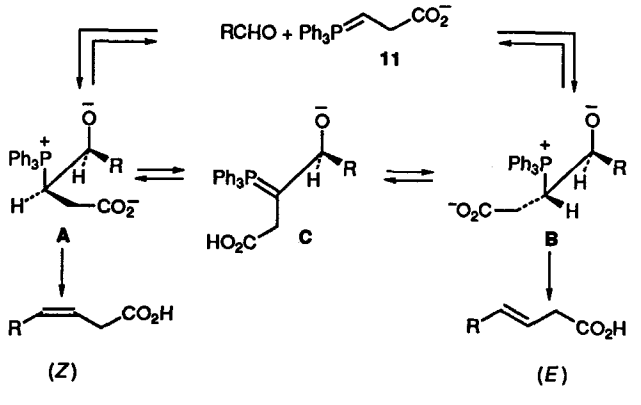
6 R = H
7 R = TBDMS
8 R = TBDMS, R′ = H
9 R = TBDMS, R′ = THP
10 R = H, R′ = THP

Scheme 1 *Reagents and conditions*: i, TBDMSCl, imidazole, DMF (98%); ii, Mg, CuBr·Me_2S, THF, then (*S*)-methyloxirane (86%); iii; 3,4-dihydro-2*H*-pyran, PPTS, CH_2Cl_2 (95%); iv; Bu^n_4NF, THF, (95%); v; PCC, AcONa, CH_2Cl_2, (~90%)

Condensation of the phosphorane $Ph_3P{=}CHCH_2CO_2^-$ with carbonyl compounds "can be very problematic".[6] In some cases this reaction completely failed[6–9] whereas a few relatively successful examples have demonstrated the predominant formation of the (*E*)-isomer.[6,8,10,11] Additionally, there are no reliable data concerning the *E*/*Z* ratio for several products prepared in this way, *cf.*[12,13]

The unusual (*E*)-stereochemistry of the Wittig reaction with β-carboxy ylides may be rationalized (Scheme 2) by either reversibility of the betaines **A** and **B** formation step or internal proton transfer to give β-oxidophosphorane **C**. As a result, accumulation of thermodynamically more stable *threo*-betaine **B** may take place followed by the preferential formation of an (*E*)-enriched olefin, *cf.*[10,11]

We found that the interaction of 0.5 mol equiv. of the freshly-prepared aldehyde **3** with the phosphorane generated from 1 mol equiv. of the phosphonium salt **5** using 1 mol equiv. butyllithium at −70 °C smoothly furnished the olefin **11** (Scheme 3) with a *Z*/*E* ratio of 84:16 in *ca.* 70% yield. If

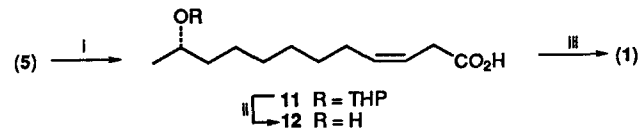


11

A **C** **B**

(*Z*) (*E*)

Scheme 2



Scheme 3 *Reagents and conditions*: i, BuLi, THF–HMPA, then **3** (63% from **10**); ii, PPTS, EtOH (95%); iii; 2-Py_2S_2, Ph_3P, $AgClO_4$, MeCN–xylenes (57%), then HPLC (73%)

2 mol equiv. of the base were used to generate the ylide (standard conditions for carboxyphosphoranes, *cf.*[8,10–13]) the stereoselectivity of the reaction essentially reduced ($Z/E \simeq 70:30$); in addition, the yield of **11** drastically dropped (30%) owing to β-elimination of the triphenylphosphine molecule, *cf.*[12] The stereochemical results thus observed may be explained by suppression of betaine **A**-oxidoylide **C**-betaine **B** interconversion due to intermolecular protonation of **A** with excess of acid **5**.

Deprotection of the THP ether **11** afforded the hydroxy-acid **12** which was subjected to macrolactonization using 2,2′-dipyridyl disulfide, triphenylphosphine and silver perchlorate under high dilution conditions, as has already been achieved for this reaction.[2,4] Unexpectedly, the yield of the target compound **1** could essentially be increased by an insignificant change in the isolation procedure. Namely, the solvent used was separated by distillation under reduced pressure whereas in earlier procedures flash-chromatography was employed for this purpose.[2,4]

The stereoisomeric composition of the compounds **12** and **1** was found to be approximately the same as noted above for **11** ($Z/E \simeq 85:15$). This ratio in all three cases was determined from ^{1}H NMR spectra by comparing integral intensities of either α-proton doublets [δ 3.12 (*Z*) and 3.06 (*E*) ppm] for β,γ-unsaturated acids **11** and **12** or methyl doublets [δ 1.23 (*Z*) and 1.20 (*E*) ppm] for the lactone **1**.

Stereochemically pure ferrulactone II ($Z \geqslant 98\%$) was obtained by HPLC [Lichrosorb Si 60 (250 × 16 mm), heptane–ethyl acetate (98:2), 5 ml min^{-1}] of the above (*Z*)-enriched product in a 73% isolated yield. The ^{1}H NMR spectrum and optical rotation of the final product **1** thus synthesized were identical to those reported earlier for this compound;[2,4] $[\alpha]_D^{20} + 99.7°$ (*c* 1.2, $CHCl_3$) {lit.,[4] $[\alpha]_D + 97.8°$ (*c* 0.57, $CHCl_3$)}. The overall yield of ferrulactone II was 19% in 8 steps from bromoalcohol **6**.

Thus, an efficient synthesis of ferrulactone II has been realized based on a readily available phosphonium salt **5** and (*S*)-methyloxirane.

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