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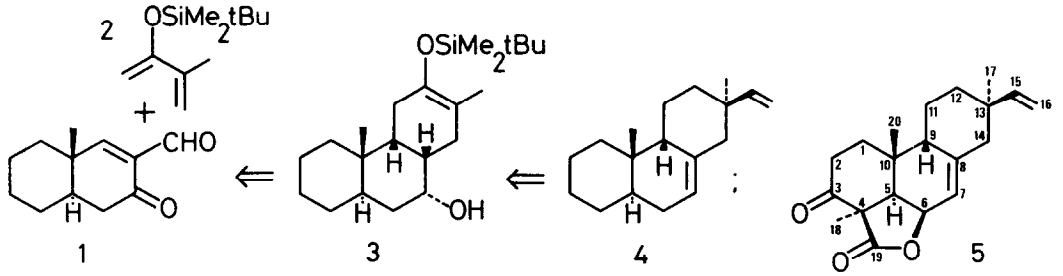
STEREOSPECIFIC PREPARATION OF (±)-4,4-DINOR-9βH-PIMARA-7,15-DIENE, A MODEL FOR THE TOTAL SYNTHESIS OF MOMILACTONE TYPE DITERPENES

A. Sicherer-Roetman, B.J.M. Jansen and Ae. de Groot*

Agricultural University, Department of Organic Chemistry
De Dreijen 5, 6703 BC Wageningen, The Netherlands

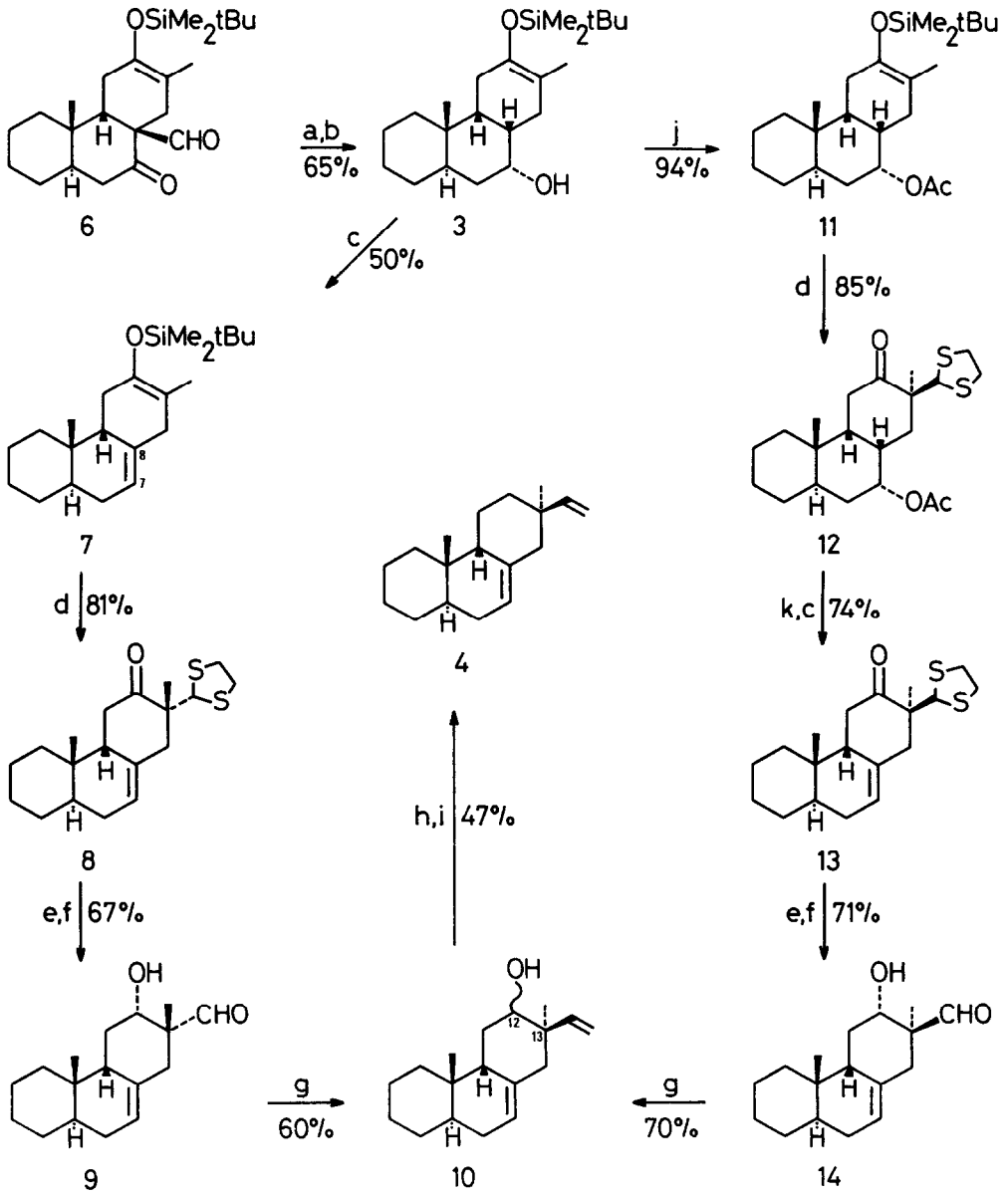
SUMMARY: The synthesis of (±)-4,4-dinor-9βH-pimara-7,15-diene, 4, a model compound for momilactones, has been achieved via stereospecific Diels-Alder reaction and alkylation.

The fungitoxic momilactone diterpenes (eg. momilactone A, 5) form a class of rather unusual natural products, possessing a trans-syn hydrophenanthrene skeleton[1,2]. Other diterpenes with similar structures are annonalide[3], icacine and analoga[4] and humirianthenolides A-F[5]. The only total synthesis of a trans-syn tricyclic diterpene reported in the literature, is the synthesis of the 9βH-pimara-8(14),15-dienes by Church and Ireland[6] in 1963. More recently, Orsini and Pelizzoni described some synthetic approaches toward annonalide[7,8,9]. As a result of our research into the synthesis of these compounds, we now wish to report the synthesis of model compound 4[10], which possesses all main features of the BC-ringsystem of the momilactones, in particular the trans-syn ring arrangement, the $\Delta^{7,8}$-double bond and the geminally disposed α-methyl and β-vinyl groups at C-13. A Diels-Alder approach, starting from formyldecalone 1, seemed particularly attractive, since it might be expected to furnish the correct stereochemistry at C-9[11,12]. When 2-silyloxybutadienes are used as dienes, an adventitious benefit is found in the regiospecific construction of a silylenolether, which is directly suitable for alkylation at C-13.



1 3 4 5

SCHEME 1



a: Triton B, MeOH, Δ; b: $LiAl(OtBu)_3H$, THF, 0^oC; c: $POCl_3$, pyridine; d: 2-ethoxy-1,3-dithiolan, $ZnCl_2$, toluene; e: $NaBH_4$, EtOH, 0^oC; f: CH_3I, H_2O, acetone, Δ; g: $Ph_3P{=}CH_2$, DMSO; h: pyridinium-chlorochromate, benzene; i: NH_2NH_2, glycol, Δ; j: Ac_2O, dimethylaminopyridine, pyridine; k: NaOMe, MeOH, Δ

The starting compound, 1, was prepared via formylation and dehydrogenation of *trans*-10-methyl-decal-3-one[13,14]. Initially we used 2-trimethylsilyloxybutadienes as diene components. The Diels-Alder reactions proceeded smoothly, but severe hydrolysis problems were encountered with the resulting adducts (cf. ref. 8). These problems were effectively overcome by the use of 2-t-butyldimethylsilyloxybutadiene 2[15]. Catalyzed by dry $ZnCl_2$, the Diels-Alder reaction was complete at ambient temperature within 4 hours in toluene as solvent and furnished in 95% yield a stable trans-syn-cis adduct, 6. Compound 6 was deformylated and the oxo group reduced. Upon reduction with $NaBH_4$ the resulting product was a 2:1 mixture of the epimeric alcohols. When $LiAl(OtBu)_3H$ was employed, the reduction proceeded stereospecifically from the least hindered side and afforded the α-alcohol 3 as the sole product. From this point on, two possible routes were investigated (Scheme 1), one via alkylation of the $\Delta^{7,8}$-compound 7 and the other via alkylation of the 7α-acetoxy compound 11. Although the route via alkene 7 is shorter, it could be expected that the alkylation reaction would produce a mixture of α- and β-alkylated products 8 and 13. On the other hand the steric hindrance of the 7α-acetoxy group in 11 should prevent α-alkylation, thus leading exclusively to the desired β-alkylated product 13.
Compound 7 was prepared by dehydration of 3, using $POCl_3$/pyridine. Alkylation of compound 7 with 2-ethoxy-1,3-dithiolan/$ZnCl_2$[16] surprisingly only gave one dithiolanyl compound, 8, which proved to have the dithiolanylgroup in the α-position. Reduction and hydrolysis[17] of 8 gave hydroxyaldehyde 9. However, during the Wittig reaction of this compound, equilibration occurred, presumably via a (retro)-aldol reaction, resulting in considerable epimerization at C-12 and C-13. Only a small amount of the α-vinyl product was found. Oxidation of 10 and Wolff-Kishner reduction of the oxogroup finally afforded the model compound 4.
A more stereospecific approach to 4 was indeed found via alkylation of the 7α-acetoxy compound 11 with 2 ethoxy-1,3-dithiolan/$ZnCl_2$. In this case the β-dithiolanyl product, 12, was formed exclusively, as was expected. Compound 12 was elaborated further as shown in Scheme 1. Here, too, some epimerization occurred at C-12 during the Wittig reaction of compound 14, but no α-vinyl product could be detected in this case.
X-ray crystallography[18] of the dithiolanyl compounds 8 and 13 and ^{13}C-NMR spectroscopy[19] of the vinyl compounds 10 and 4 were used to establish unambiguously the depicted stereochemistry of these products, especially at C-13. This stereospecific synthesis of model compound 4 opens up the way to the total synthesis of diterpenes possessing a trans-syn hydrophenanthrene skeleton.

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10. This and subsequent products are pairs of enantiomers. All intermediates had mass, NMR and IR spectra in accord with their expected structures. Elemental analysis and/or exact mass measurements provided correct results for all new compounds.
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