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THE STEREOSELECTIVE SYNTHESIS OF (±)-9βH-PIMARA-7,19-DIENE

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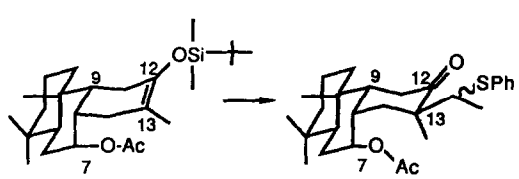
Abstract. The trans-syn-cis tricyclic system, present in (±)-9βH-pimara-7,19-diene (**8**) was formed via a Diels-Alder reaction of enone aldehyde **2** with 2-(tert-butyldimethylsilyloxy)-3-methyl-1,3-butadiene. The resulting regiospecific silyl enol ether was deformylated, reduced and acetylated to the acetate **4**. Stereoselective alkylation of the silyl enol ether with [(1-chloroethyl)thio]benzene followed by oxidation and elimination of the sulfoxide group, gave **6** with the β-oriented vinyl group at C-13. A Wolff-Kishner reduction followed by dehydration afforded the title compound **8**.

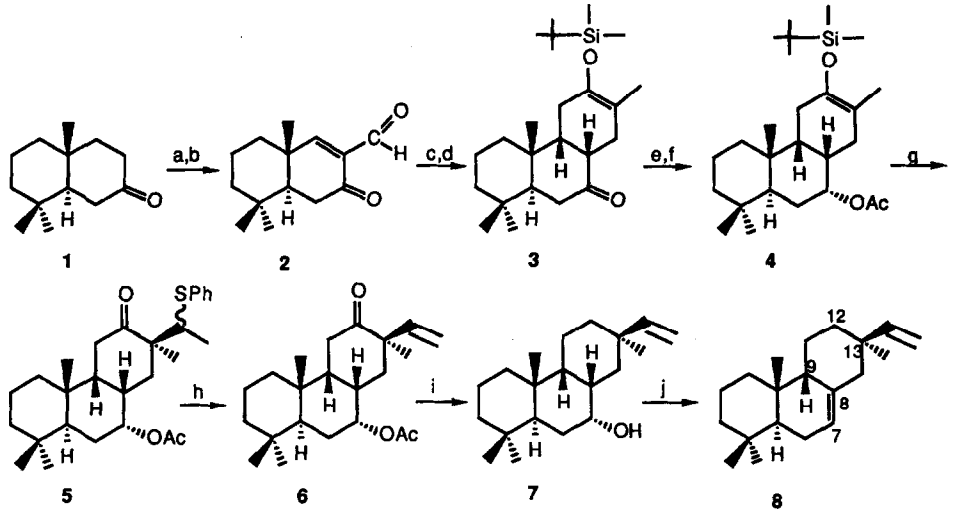
Diterpenes with a 9βH-pimarane skeleton belong to a rather unusual class of natural products possessing a trans-syn perhydrophenanthrene system. Examples of such pimaranes are the momilactones A, B and C[1], annonalide[2] and icaceine[3]. As part of our investigations into the total synthesis of these compounds we now report on the synthesis of (±)-9βH-pimara-7,19-diene (**8**) which is probably one of the intermediates in the biosynthesis of photoalexines in rice[4].

Our synthetic approach is based upon the Diels-Alder reaction of enone aldehyde **2** with 2-(tert-butyldimethylsilyloxy)-3-methyl-1,3-butadiene. It was shown before[5,6] that this approach gives the correct stereochemistry at C-9 and in addition it provides the desired regiospecific silyl enol ether which is directly suitable for alkylation at C-13. In our former study it was shown that the acetate group at C-7 prevents alkylation of the silyl enol ether **4** from the α-side thus securing the introduction of the vinyl precursor at C-13 from the desired β-side. The same acetate group at C-7 can be used lateron for the introduction of the $\Delta^{7,8}$ double bond.



4 **5**

The Diels-Alder reaction of the enone aldehyde **2** and 2-(tert-butyldimethylsilyloxy)-3-methyl-1,3-butadiene proceeded smoothly at room temperature with $ZnCl_2$ as catalyst in nearly



a, NaH, HCOOEt; b, PhSeCl, pyr., H_2O_2; c, $H_2C{=}C(OSiMe_2tBu)C(CH_3){=}CH_2$, $ZnCl_2$; d, NaOEt, HOEt; e, $LiAl(OtBu)_3H$; f, Ac_2O, pyr., DMAP; g, $H_3CCHClSPh$, $SnCl_4$; h, $NaIO_4$, Δ ; i, $H_2N\text{-}NH_2$, KOH, Δ; j, $POCl_3$, pyr.

quantitatieve yield. When 3-methyl-2-trimethylsilyloxy-1,3-butadiene was used, the initially formed trimethylsilyl enol ether proved to be extremely labile and it was hydrolized very fast. This problem was effectively overcome by the use of a tert-butyl-dimethylsilyloxy enol ether. The stereoselective reduction of the carbonyl group at C-7 was accomplished using tri-tert-butoxyaluminium hydride and the resulting alcohol was acetylated with acetic anhydride and 4-(dimethylamino)pyridine as catalyst.

In our former approach the silyl enol ether was alkylated with 2-ethoxy-1,3-dithiolane as a precursor for the vinyl group. In this case a roundabout way involving reduction, reoxidation and finally complete reduction of the carbonyl group at C-12, proved necessary to achieve the desired situation at C-13 and C-12. We now have effected a substantial simplification for the introduction of the vinylgroup via Paterson alkylation of the silyl enol ether **4** with [(1-chloroethyl)thio]benzene[7]. This reaction proceeded in 80% yield using $SnCl_4$ as catalyst and again the correct stereochemistry at C-13 was achieved. Oxidation of the sulfide in **5** and elimination of the sulfoxide group provided the vinylgroup in **6**, now in a straightforward way. The Wolff-Kishner reduction of the carbonylgroup in **6** simultaneously gave the expected and desired saponifiaction of the acetate at C-7. Dehydration of the alcohol **7** with $POCl_3$ in pyridine finally yielded 9βH-pimara-7,19-diene (**8**) in 28% overall yield from decalone **1**.

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EXPERIMENTAL PART

Boiling points and melting points are uncorrected. Routine ^1H NMR spectra were recorded on a Varian EM-390 spectrometer, ^{13}C NMR spectra and 300 MHz ^1H NMR spectra were recorded using a Bruker CXP-300 spectrometer. Chemical shifts are reported in ppm downfield relative to tetramethylsilane (δ scale). $CDCl_3$ was used as solvent unless stated otherwise. Mass spectral data and high resolution mass measurements were obtained using an AEI-MS-902 spectrometer. Elemental analyses were carried out using a Carlo Erba Elemental Analyser 1106. Aqueous solutions were usually extracted three times with ether. The combined ethereal extracts were dried on magnesium sulfate prior to filtration and evaporation of the solvent under reduced pressure. Flash chromatography was performed on silica gel (230-400 mesh). The petroleum ether used as eluens had a boiling range of 40-60°C. Solvents were purified and dried by standard methods.

cis-4a-cisoid-4a,4b-trans-4b-3-(tert-Butyldimethylsilyloxy)-1,4,4a,4b,5,6,7,8,8a,10a-decahydro-2,4bβ,8,8-tetramethylphenanthrene-10(9H)-on (3)
A mixture of 11.0 g (50 mmol) of 2[10] and 11.2 g (56 mmol) of 2-(tert-butyldimethylsilyloxy)-3-methyl-1,3-butadiene[11] was stirred for 16 h at room temperature with 7.75 g (57 mmol) of dry $ZnCl_2$ in 150 ml of toluene in a N_2 atmosphere. The catalyst was filtered off and the solvent evaporated under reduced pressure. This afforded 19.85 g (95%) of spectroscopically pure adduct as a yellow oil. ^1H NMR (CCl_4): δ 0.10 (s, 3H); 0.13 (s, 3H); 0.82 (s, 3H); 0.87 (s, 3H); 0.90 (s, 9H); 1.10 (s, 3H); 1.52 (s, 3H); 1.10-2.00 (m, 10H); 2.15-2.30 (m, 4H); 9.43 (s, 1H). HRMS: Calcd ($M^{+\cdot}$) m/e 418.2903, found 418.2906.

The adduct was dissolved in 250 ml of methanol and treated with 5.4 g (100 mmol) of sodium methoxide at room temperature. After 16 h the methanol was evaporated under reduced pressure. The residue was dissolved in water and worked up as usual. Flash chromatography eluting with petroleum ether/ether (96/4) yielded 3 (18.3 g, 94%) as a colourless oil. ^1H NMR (CCl_4): δ 0.10 (s, 3H); 0.13 (s, 3H); 0.82 (s, 3H); 0.84 (s, 3H); 0.90 (s, 9H); 1.25 (s, 3H), 1.53 (s, 3H); 1.10-2.00 (m, 10H); 2.00-2.30 (m, 4H); 2.75 (br.s, 1H). HRMS: Calcd ($M^{+\cdot}$) m/e 390.2954, found 390.2955.

cis-4a-cisoid-4a,4b-trans-4b-10α-Acetoxy-3-(tert-butyldimethylsilyloxy)-1,4,4a,4b,5,6,7,8,8a,9,10,10a-dodecahydro-2,4bβ,8,8-tetramethylphenanthrene (4)
A solution of 10.0 g (25.6 mmol) of 3 in 250 ml of dry THF was added over 10 min to a stirred solution of 7.62 g (30 mmol) lithium tri-tert-butoxyaluminium hydride in 100 ml of dry THF at 0°C. After 16 h 3 ml of water, 6 ml of 4N sodium hydroxide and 3 ml of water were added successively. The mixture was dried by adding magnesium sulfate directly. The crude product, obtained after filtration and evaporation of the solvent was used as such in the next reaction. The product, 10.2 g (100%), appeared to be spectroscopically pure. ^1H NMR (CCl_4): δ 0.03 (s, 3H); 0.06 (s, 3H); 0.77 (s, 3H); 0.85 (s, 3H); 0.96 (s, 9H); 1.00 (s, 3H); 1.50 (s, 3H); 1.10-2.20 (m, 16H); 3.82 (dd, J=3, 4.5 Hz, 1H). HRMS: Calcd ($M^{+\cdot}$) m/e 392.3110, found 392.3109.

The unpurified alcohol was dissolved in a mixture of 50 ml of pyridine and 50 ml of acetic anhydride and 200 mg of 4-dimethylaminopyridine was added. The reaction mixture was stirred for 48 h at room temperature, the solvents were evaporated under reduced pressure and the residue was dissolved in water. This mixture was worked up as usual and purified by flash chromatography on silica gel eluting with petroleum ether/ether (98/2). A yield of 8.29 g (75%) of the acetate 4 was obtained as a white crystalline solid, mp 71-72°C. ^1H NMR (CCl_4): δ 0.10 (s, 3H); 0.13 (s, 3H); 0.77 (s, 3H); 0.85 (s, 3H); 0.91 (s, 9H); 1.01 (s, 3H); 1.45 (s, 3H); 1.10-2.10 (m, 15H); 5.12 (br.s, 1H). HRMS: Calcd ($M^{+\cdot}$) m/e 434.3216, found 434.3219. Anal: $C_{26}H_{46}O_3Si$ calcd C 71.84, H 10.67; found C 71.57, H 10.69.

cis-4a-cisoid-4a,4b-trans-4b-10α-Acetoxy-perhydro-2α,4bβ,8,8-tetramethyl-2β-vinyl-phenanthrene-3-one (6)
A solution of 1.93 g (4.4 mmol) of 4 and 0.76 g (4.4 mmol) of [(1-chloroethyl)thio] benzene[12] in 25 ml of dry dichloromethane was treated with 1.16 g (4.4 mmol, 520 µl) of tin tetrachloride at -80°C. After 15 min 5 ml of triethylamine was added, followed by 10 gram of silica gel. This mixture was evaporated till dryness and purified by flash chromatography on silica gel eluting with petroleum ether/ether (90/10). A stereoisomeric mixture of sulfides was obtained in 80% yield. ^1H NMR (major isomer): δ 0.80 (s, 6H); 1.07 (s, 6H); 1.23 (d, J=7Hz, 3H); 1.10-2.00 (m, 11H); 1.97 (s, 3H); 2.10-3.00 (m, 4H); 3.43 (q, J=7Hz, 1H); 5.00 (br.s, 1H); 7.10-7.50 (m, 5H). HRMS (major isomer): Calcd ($M^{+\cdot}$) m/e 456.2698, found 456.2701. ^1H NMR (minor isomer): δ 0.80 (s, 6H); 1.07 (s, 3H); 1.15 (s, 3H); 1.30 (d, J=7Hz, 3H); 1.10-2.00 (m, 11H); 1.97 (s, 3H); 2.10-3.00 (m, 4H); 3.43

(q, J=7Hz, 1H); 5.00 (br.s, 1H); 7.10-7.50 (m, 5H). HRMS (minor isomer): Calcd ($M^{+\cdot}$) m/e 456.2698, found 456.2699.

The mixture of sulfides, 1.62 g (3.55 mmol), was dissolved in 250 ml of methanol/water (90/10). Sodium periodate, 0.76 g (3.55 mmol), was added and the reaction mixture was stirred for 24 h at room temperature. The solvents were evaporated under reduced pressure and the residue was dissolved in dichloromethane. The solution was washed with water and the dichloromethane was evaporated. The crude mixture of isomeric sulfoxides was dissolved in toluene and refluxed for 2 h. The reaction mixture was worked up as usual and the residu was purified by flash chromatography on silica gel eluting with petroleum ether/ether (90/10). This afforded 1.00 g (82%) of **6** as a colourless oil. ^{1}H NMR: δ 0.77 (s, 6H); 1.03 (s, 6H); 1.10-2.00 (m, 12H); 1.94 (s, 3H); 2.00-2.50 (m, 3H); 4.93 (dd, J=1.5, 7Hz, 1H); 4.99 (br.s, 1H); 5.12 (dd, J=1.5, 14Hz, 1H); 5.90 (dd, J=9,17Hz, 1H). HRMS: Calcd ($M^{+\cdot}$) m/e 346.2508, found 346.2520.

cis-4a-cisoid-4a,4b-trans-4b-Perhydro-2α,4bβ,8,8-tetramethyl-2β-vinylphenanthrene-10α-ol (7)
A solution of 100 mg (0.29 mmol) of **6** and 0.5 g (10 mmol) of hydrazine hydrate in 5 ml of diethylene glycol was stirred for 2 h at 120°C in a nitrogen atmosphere. Water and excess hydrazine hydrate were then distilled off under reduced pressure. Two pellets of potassium hydroxide were added and the mixture was stirred for 2 h at 180°C. After cooling, water was added and the reaction mixture was worked up as usual. After purification by flash chromatography eluting with petroleum ether/ether (95/5), a yield of 70 mg (87%) of **7** was obtained as a colourless oil. ^{1}H NMR: δ 0.79 (s, 3H); 0.86 (s, 3H); 1.00 (s, 3H); 1.10 (s, 3H); 1.10-2.05 (m, 16H); 3.90 (br.s, 1H); 4.78 (dd, J=6, 1Hz, 1H); 4.94 (dd, J=12, 1Hz, 1H); 5.85 (dd, J=10, 17Hz, 1H). HRMS: Calcd ($M^{+\cdot}$) m/e 290.2610, found 290.2604.

cisoid-4a-4b-trans-4b-1,2,3,4,5,6,7,8,8a,9-Dodecahydro-2α,4bβ,8,8-tetramethyl-2β-vinylphenanthrene (8). [9βH-Pimara-7,19-diene(8)]
A solution of 40 mg (0.13 mmol) of alcohol **7** in 5 ml of pyridine was treated with 0.2 ml of phosphorus oxychloride at 0°C. After 10 min the reaction mixture was diluted with 100 ml of water and acidified with 5 ml of concentrated hydrochloric acid. After the usual work up procedure the residue was purified by flash chromatography using petroleum ether as eluent.
A yield of 30 mg (80%) of **8** was obtained as a colourless oil. ^{1}H NMR (300 MHz): δ0.89 (s, 3H); 0.90 (s, 3H); 0.91 (s, 3H); 0.94 (s, 3H); 1.10-2.0 (m, 16H); 4.86 (dd, J=11, 1Hz, 1H); 4.93 (dd, J=18, 1Hz, 1H); 5.31 (br.d, J=6Hz, 1H); 5.83 (dd, J=18, 11Hz, 1H). ^{13}C NMR: δ 18.85 (t); 21.88 (q); 22.13 (q); 22.72 (q); 23.85 (t); 25.01 (t); 32.89 (s); 33.50 (q); 35.24 (s); 36.84 (t); 37.94 (t); 38.82 (s); 43.11 (t); 43.67 (d); 48.11 (t); 55.33 (d); 109.07 (t); 119.93 (d); 136.81 (s); 150.54 (d). MS m/e 272 ($M^{+\cdot}$, 100); 257 (77); 243 (22); 229 (16); 203 (18); 187 (23); 161 (18); 148 (46); 133 (25); 124 (25); 119 (32); 109 (52); 105 (34).
HRMS: Calcd ($M^{+\cdot}$) m/e 272.2504, found 272.2504.

REFERENCES

1a M. Tsunakawa, A. Ohba, N. Sasaki, C. Kabuto, T. Kato, Y. Kitahara and N. Takahashi, *Chemistry Letters*, **1976**, 1156.
b T. Kato, H. Aizawa, M. Tsunakawa, N. Sasaki, Y. Kitahara and N. Takahashi, *J. Chem. Soc., Perkin I*, **1977**, 250.
2 F. Orsini, F. Pellizoni, A.T. McPhail, K.D. Onan and E. Wenkert, *Tetrahedron Letters*, **1977**, 1085.
3. P. On'okoko and M. van Haelen, *Phytochemistry*, **1980**, *19*, 303.
4. R.M. Coates and C.A. West, personal communication.
5. A. Sicherer-Roetman, B.J.M. Jansen and Ae. de Groot, *Tetrahedron Letters*, **1984**, *25*, 2593.
6. A. Sicherer-Roetman, B.J.M. Jansen and Ae. de Groot, *Rec. Trav. Chim. Pays Bas*, **1985**, *104*, 193.
7. I. Paterson, *Tetrahedron*, **1988**, *44*, 4207.
8. Recently we have developed the synthesis of enantriomerically pure decalone **1**, starting from carvone[9]. This also enables the synthesis of enantiomerically pure pimaranes following the procedure described in this paper.
9. B.J.M. Jansen, J.A. Kreuger and Ae. de Groot, *Tetrahedron*, in press.
10. W.L. Meijer, G.B. Clemans and R.A. Manning, *J. Org. Chem.*, **1975**, *40*, 3686.
11. R.E. Ireland and W.J. Thompson, *J. Org. Chem.*, **1979**, *44*, 3041.
12. R. Tanikaga, K. Miyashita, N. Ono and A. Koji, *Synthesis*, **1982**, 131.