Highly Stereocontrolled Synthesis of (±)-3-Oxosilphinene *via* Intramolecular Diels–Alder Reaction

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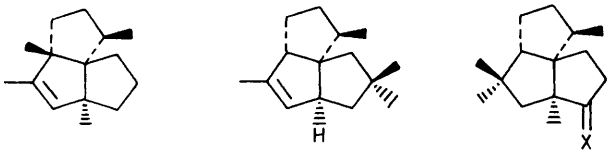
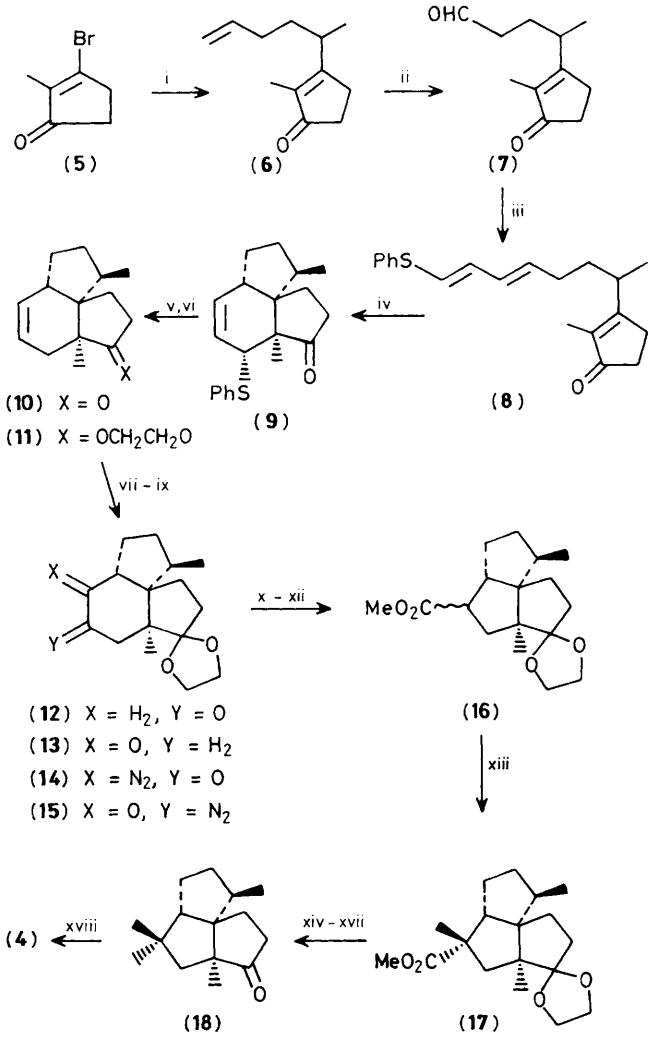
The angularly fused triquinane, (±)-3-oxosilphinene (**4**), was stereoselectively synthesised *via* an intramolecular Diels–Alder reaction as the key step.

Angular tricyclopentanoid sesquiterpenes, such as isocomene (**1**), pentalenene (**2**), and silphinene (**3**), have received a great deal of attention recently from synthetic chemists because of their unique structures.[1] During our synthetic studies on natural products using intramolecular cycloaddition, a general synthetic route to such compounds *via* tricyclo-[7.3.0.0^{1,5}]dodecene derivatives was planned. According to this strategy, we have studied the total synthesis of 3-oxosilphinene (**4**), isolated from *Dugaldia hoopesii*,[2,3] and report a fully stereocontrolled synthesis of its racemate.

Reaction of the Grignard reagent derived from 5-bromohex-1-ene[4] with 3-bromo-2-methylcyclopent-2-enone (**5**)[5] in the presence of CuBr led to addition–elimination to produce quantitatively the enone (**6**).† Oxidation of (**6**) with OsO_4 and $NaIO_4$[6] gave the aldehyde (**7**),† which was stereoselectively converted into monosubstituted (*E*)- and (*Z*)-dienes by Yamamoto's methods.[7] An intramolecular Diels–Alder reaction carried out by heating an *o*-dichlorobenzene solution of the (*E*)-diene, obtained in 17% yield by the action of allyldiphenylphosphine oxide, hexamethylphosphoric triamide (HMPA), and Bu^{n}Li on (**7**), led to the tricyclo[7.3.0.0^{1,5}]dodecene (**10**)† as a single product in 45% yield, while the (*Z*)-diene, obtained in 51% yield from (**7**) by reaction with allyldiphenylphosphine, Bu^{t}Li, Ti(O^{i}Pr)$_4$, and then MeI, yielded no cyclised product. It was assumed that the product (**10**) from the (*E*)-isomer, formed *via* the *exo*-mode intermediate, would be correctly arranged with four contiguous asymmetric centres around the spiro carbon atom. This assumption was confirmed by the conversion of (**10**) into the natural sesquiterpene (**4**).



Scheme 1



Scheme 2. Reagents, conditions, and yields: i, CH_2=$CH[CH_2]_2$-$CHBrMe$, Mg, CuBr, THF–Et_2O, −20 to 20 °C, 100%; ii, OsO_4, $NaIO_4$, Et_2O–H_2O, 79%; iii, $(EtO)_2P(:O)CH_2CH$=$CHSPh$, Bu^{n}Li, THF, −78 to 20 °C, 78%; iv, *o*-$Cl_2C_6H_4$, 200—220 °C, 15 h, 76%; v, Ca, NH_3, Et_2O, 98%; vi, PCC on alumina, CH_2Cl_2, 88%; vii, $(HOCH_2)_2$, TsOH, benzene, reflux, 91%; viii, BH_3·Me_2S, n-hexane, then H_2O_2, NaOH; ix, CrO_3–2 pyridine, CH_2Cl_2, 78% from (**11**); x, HCO_2Et, NaH, MeOH, Et_2O; xi, TsN_3, Et_3N, CH_2Cl_2; xii, *hv*, MeOH, 60% from the mixture of (**12**) and (**13**); xiii, LDA; MeI, THF, −78 to 20 °C, 80%; xiv, DIBAL, Et_2O, −78 to 20 °C, 100%; xv, CrO_3–2 pyridine, CH_2Cl_2, 84%; xvi, NH_2NH_2·H_2O, NaOH, diethylene glycol, 120—185 °C, 99%; xvii, 3.6% HCl, acetone, 87%; xviii, LDA; Me_3SiCl, THF, −78 °C then, $Pd(OAc)_2$, *p*-benzoquinone, MeCN, 82%.

Abbreviations: THF = tetrahydrofuran; PCC = pyridinium chlorochromate; Ts = *p*-$MeC_6H_4SO_2$; LDA = $LiNPr^i_2$; DIBAL = Bu^i_2AlH.

† I.r. ($CHCl_3$) and n.m.r. ($CDCl_3$, 100 MHz) data: (**6**) i.r. 1690 cm^{-1} (C=O); n.m.r., δ 1.12 (3H, d, *J* 7 Hz, Me), 1.68 (3H, s, Me), and 4.75—6.27 (3H, m, CH=CH_2); (**7**) i.r. 1730 and 1695 cm^{-1} (C=O); n.m.r. δ 1.12 (3H, d, *J* 7 Hz, Me), 1.68 (3H, s, Me), and 9.63 (1H, br. s, CHO); (**8**) i.r. 1680 cm^{-1} (C=O); n.m.r. δ 1.13 (3H, d, *J* 7 Hz, Me), 1.65 (3H, s, Me), 5.83—6.40 (4H, m, olefinic H), and 7.28—7.63 (5H, m, Ph); (**9**) i.r. 1735 cm^{-1} (C=O); n.m.r. δ 1.09 (3H, d, *J* 7 Hz, 2-Me), 1.19 (3H, s, 9-Me), 3.98 (1H, br. d, *J* 5 Hz, 8-H), and 5.72—5.82 (2H, m, olefinic H); (**10**) i.r. 1735 cm^{-1} (C=O); n.m.r. δ 0.98 (3H, s, 9-Me), 1.08 (3H, d, *J* 7 Hz, 2-Me), and 5.57 (2H, br. s, olefinic H); (**16**) i.r. 1725 cm^{-1} (C=O); n.m.r. δ 0.93 (3H, d, *J* 6 Hz, 2-Me), 0.94 (3H, s, 8-Me), 2.20—2.42 (1H, m, 6-H), 3.63 (3H, s, OMe), and 3.89 (4H, br. s, OCH_2CH_2O); (**17**) i.r. 1725 cm^{-1} (C=O); n.m.r. δ 0.95 (3H, d, *J* 6 Hz, 2-Me), 1.03 and 1.25 (each 3H, s, 6- and 8-Me), 3.60 (3H, s, OMe), and 3.88 (4H, br. s, OCH_2CH_2O); (**18**) i.r. 1725 cm^{-1} (C=O); n.m.r. δ 0.84, 0.90, and 0.92 (each 3H, s, 3 × Me), 0.99 (3H, d, *J* 6 Hz, 2-Me), and 2.32—2.52 (2H, m, 10-H_2).

The transformation of (**7**) to (**10**) was effectively performed *via* cycloaddition of the corresponding sulphenyl derivative. Thus the aldehyde (**7**) was condensed with diethyl 3-phenylthioprop-2-enylphosphonate[8] in the presence of Bu^nLi to afford the diene (**8**),† intramolecular cycloaddition of which gave the tricyclic compound (**9**),† needles, m.p. 97—99 °C, as the sole product in 59% overall yield. The sulphenyl group was readily removed by two steps: reduction using metallic Ca in liquid ammonia[9] and oxidation of the epimeric alcohols with PCC on alumina.[10] The product (**10**) was identical with the above compound directly prepared.

Ring contraction was achieved by Wolff rearrangement[11] of the mixture of diazo ketones (**14**) and (**15**). After protection of the ketone (**10**) as the ethylene acetal, the resulting alkene was subjected to hydroboration–oxidation and subsequent oxidation using CrO_3–pyridine[12] to afford a separable mixture of the two ketones (**12**) and (**13**) in a ratio of 3 : 2. Formylation of the mixture of (**12**) and (**13**), followed by diazo-exchange and irradiation of the mixture of (**14**) and (**15**) with a 400 W high-pressure mercury lamp through a Pyrex filter in MeOH furnished the tricyclo[6.3.0.$0^{1,5}$]undecane derivative (**16**).†

Methylation of (**16**) using $LiNPr^i_2$ and MeI took place selectively from the less hindered β-side to provide the trimethyl compound (**17**)† as a single product. The methoxycarbonyl group was converted into methyl by the standard procedure: reduction with Bu^i_2AlH, oxidation with CrO_3–pyridine, and Wolff–Kishner reduction. After deprotection, the resulting ketone (**18**)† was silylated and then oxidised with $Pd(OAc)_2$ in the presence of *p*-benzoquinone[13] to furnish (±)-3-oxosilphinene (**4**), needles, m.p. 50—51 °C, whose n.m.r., i.r., and mass spectra were consistent with reported data.[2] Thus the first total synthesis of the racemate of the natural product was accomplished in a highly stereoselective manner.

We thank Dr. H. Seto, the Institute of Physical and Chemical Research, for 400 MHz ^1H n.m.r. spectra of (±)-3-oxosilphinene.

Received, 27th January 1986; Com. 119

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