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SYNTHESIS OF (±)-SENOXEPIN - THE FIRST NATURALLY OCCURRING ANTI-HÜCKEL OXEPIN DERIVATIVE

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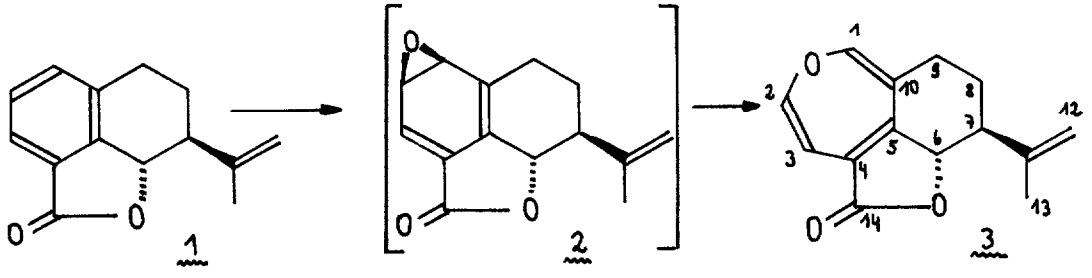
Abstract: The first total synthesis of (±)-senoxepin **3** is described. **3** is prepared via an intramolecular [4+2] cycloaddition from a substituted decadienyne **7**. The resulting hexalin **8** was converted to a lactone, which on epoxidation, NBS bromination and elimination with NaI afforded senoxepin.

Arene oxides have been postulated as biogenetic intermediates in the formation of phenols.[1] Accordingly, their antiaromatic valence tautomers, oxepins, are expected to occur as natural products in case structural features favour the oxepin tautomer. So far only one compound of that type has been isolated from nature, the so called senoxepin **3**, a norsesquiterpenelactone present in *Senecio platyphylloides*, accompanied by its biogenetic precursor platyphyllide **1**.[2,3]



Most likely due to the presence of an electron acceptor and the two annellated saturated rings,[4,5,6] the equilibrium lies on the side of the oxepin, no trace of the arene oxide **2** was observed.[2]

A model compound lacking the isopropenyl moiety was synthesized via the corresponding hexalin epoxide.[7] A similar concept would require the substituted decadienyne **7**. That ester was synthesized as a mixture of epimers starting with methyl 3,5-hexadienoate, readily obtainable by isomerization of methyl sorbate.[8] Alanate reduction furnished the corresponding alcohol, which was transformed to the tosylate **5**. Alkylation of methyl acetoacetate yielded the *C*-alkylated product exclusively. Boranate reduction,

followed by transacetalization with dimethoxymethane in the presence of thionylchloride in chloroform afforded almost quantitatively the ester **6**. Subsequent alanate reduction, PCC oxidation and coupling with the lithium derivative of methyl propiolate, followed by acetylation gave as expected four epimers of **7**, which could partly be separated by flash chromatography (two Cram and two anti-Cram products, ca. 3 : 2). On heating the mixture in toluene for two days, the hexalin derivative **8** was obtained in 81 % yield. The ^{1}H NMR spectrum indicated the presence of eight racemates which, however, could be transformed in 68 % yield to a single racemic lactone **9** by heating in THF/water with $Ba(OH)_2$ for one day, acetal hydrolysis and PCC oxidation {**^{1}H NMR of 9**, $CDCl_3$: δ 2.91 (m, H-3), 5.84 (dddd, H-4), 5.70 (dddd, H-5), 3.07 (m, H-5a), 2.23 (dddd, H-6*eq*), 1.19 (dddd, H-6*ax*), 1.55 (dddd, H-7*ax*), 2.00 (dddd, H-7*eq*), 2.45 (ddd, H-8), 5.02 (br d, H-8a), 2.29 (s, Me), J [Hz]: 3-4 = 3.5, 3-5 = 2.5, 3'-4 = 3.0, 3'-5 = 2.5, 4-5 = 10.0, 4-5a = 2.0, 5-5a = 2.5, 5a-6*eq* = 6.5, 5a-6*ax* = 13.0, 6*eq*-6*ax* = 12.5, 6*eq*-7*ax* = 3.5, 6*eq*-7*eq* =3.0, 6*ax*-7*ax* = 13.0, 6*ax*-7*eq* = 3.5, 7*ax*-7*eq* = 14.5, 7*ax*-8 = 12.5, 7*eq*-8 = 3.5, 8-8a = 10.0}. Most likely the transesterification of **8** is accompanied by epimerization via enolization at C-4a and C-8. Inspection of models further indicated that lactonization required *cis* orientation of H-4a and H-8.

Conversion of **9** to oxepin **13** was accomplished by epoxidation, followed by double NBS bromination and reaction with sodium iodide[9] {**^{1}H NMR of 13**, $CDCl_3$: δ 5.86 (br dd, H-1), 5.99 (dd, H-2), 6.05 (d, H-3), 5.12 (br d, H-6), 2.56 (ddd, H-7), 1.77 (dddd, H-8*ax*), 2.07 (dddd, H-8*eq*), 2.67 (br ddd, H-9*eq*), 2.28 (dddd, H-9*ax*), 2.32 (s, Me), J [Hz]: 1-2 = 0.9, 1-9*ax* = 2.5, 2-3 = 5.2, 6-7 = 10.7, 7-8*ax* = 12.6, 7-8*eq* = 3.0, 8*ax*-8*eq* = 14.5, 8*ax*-9*eq* = 4.8, 8*ax*-9*ax* = 13.0, 8*eq*-9*eq* = 2.5, 8*eq*-9*ax* = 5.2, 9*eq*-9*ax* = 13.5}. However, it showed to be impossible to introduce the missing methylene group without destroying the oxepin moiety. Applying Oshima's carbonyl methylenation conditions ($CH_2Br_2/Zn/TiCl_4$)[10] to **13** afforded in 98 % yield platyphyllide **1**, the biogenetic precursor of **3**.

Thus a two step methylenation reaction was required, permitting the final transformation to senoxepin under very mild conditions. Therefore, the Peterson reaction[11] was chosen. Addition of trimethylsilylmethylmagnesium chloride to **9** afforded a 2 : 1 mixture of two epimeric β-hydroxysilanes, separable by flash chromatography. The main compound, subjected to epoxidation, NBS bromination and stirring in acetone with sodium iodide yielded 22 % of (±)-senoxepin **3**, while the epimeric β-hydroxysilane untimely eliminated trimethylsilanol on treatment with *m*-chloroperbenzoic acid. The spectral data of racemic **3** were found to be identical with those of the natural product. **^{1}H NMR of 3**, $CDCl_3$: δ 5.84 (br dd, H-1), 5.98 (dd, H-2), 6.04 (d, H-3), 4.90 (d, H-6), 2.11 (br ddd, H-7), 1.64 (dddd, H-8*ax*), 1.96 (dddd, H-8*eq*), 2.64 (dddd, H-9*eq*), 2.28 (dddd, H-9*ax*), 4.96 (br s, H-12), 4.93 (br s, H-12'), 1.84 (br s, Me), J [Hz]: 1-2 = 1.0, 1-9*ax* = 2.5, 1-9*eq* = 0.5, 2-3 = 5.5, 6-7 = 11.5, 7-8*ax* = 12.3, 7-8*eq* = 2.6, 8*ax*-8*eq* = 14.1, 8*ax*-9*eq* = 4.7, 8*ax*-9*ax* = 13.7, 8*eq*-9*eq* =2.6, 8*eq*-9*ax* = 5.0, 9*eq*-9*ax* = 16.0, **^{13}C NMR of 3**, $CDCl_3$ (C-1 - C-14): δ 142.8 d, 138.4 d, 110.8 d, 124.3 s, 160.3 s, 81.2 d, 48.9 d, 24.3 t, 27.3 t, 124.0 s, 143.9 s, 112.8 t, 20.4 q, 170.7 s.

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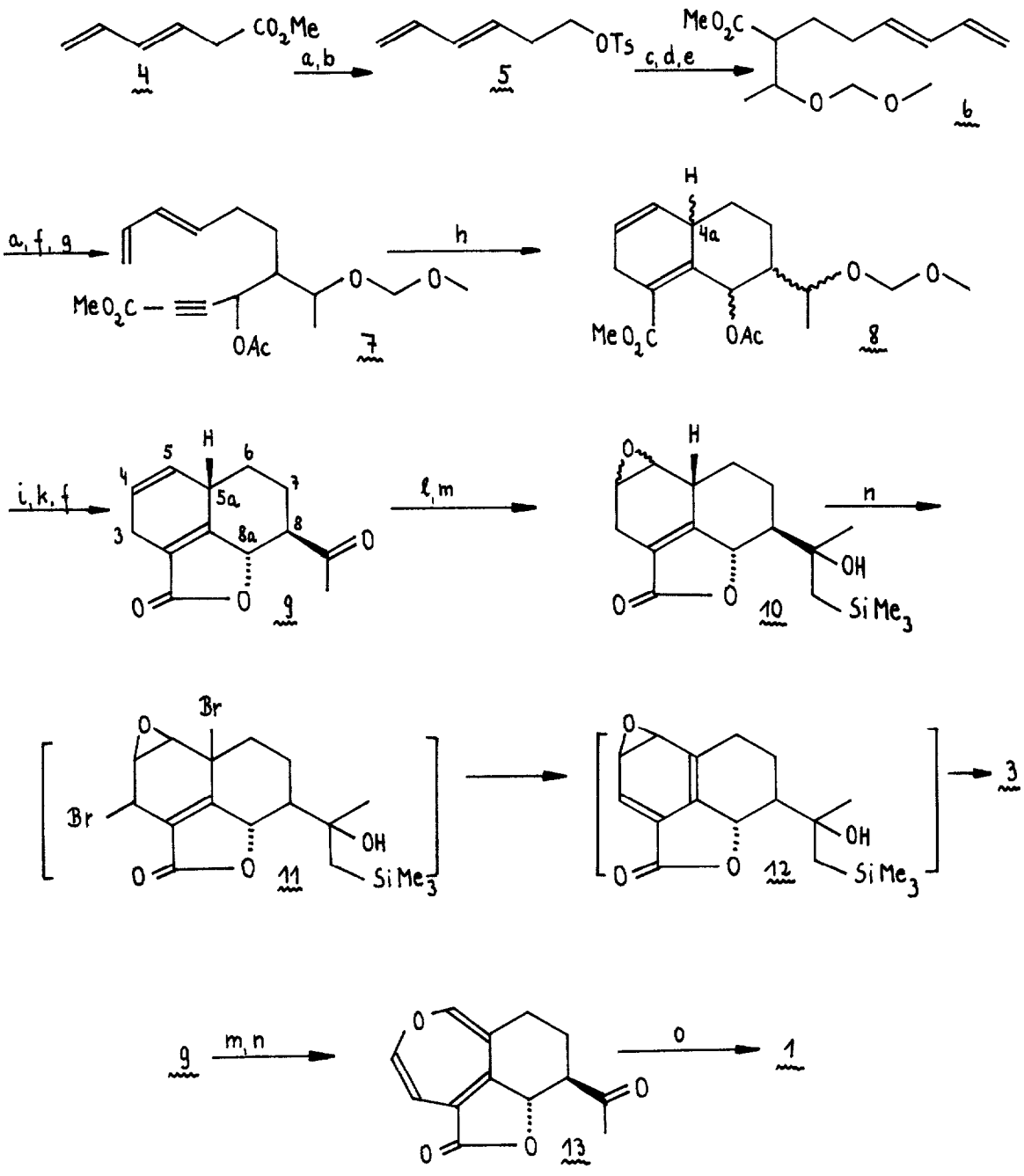

a) $LiAlH_4$, 93-98 %; b) TsCl/Pyr., 87 %; c) $MeCOCH_2CO_2Me$, NaH, DME, 3d, 96 %; d) $NaBH_4$, EtOH, 74 %; e) $CH_2(OMe)_2$, $SOCl_2$, $CHCl_3$, 98 %; f) PCC, CH_2Cl_2, 74-88 %; g) $LiC{\equiv}CCO_2Me$, then AcCl, 80 %; h) toluene, 2d, 110°C, 81 %; l) $Ba(OH)_2$, H_2O/THF, 1d, 65°C, 68 %; k) HCl/MeOH, 98 %; l) Me_3SiCH_2MgCl, 48 %; m) MCPBA, CH_2Cl_2, 1d, 40°C, 82 %; n) NBS, AIBN, CCl_4, 90 min, 65°C, then NaI, acetone, 1d, 22 %; o) CH_2Br_2, Zn, $TiCl_4$/THF, 3h, 98 %.

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