The enantioselective total synthesis of (−)-myltaylenol

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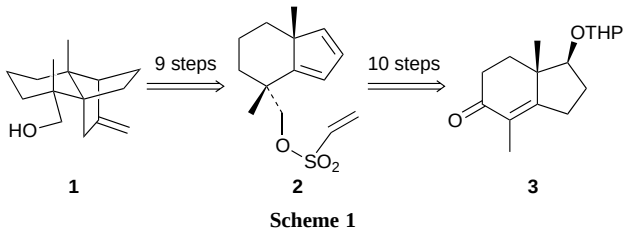
Using an intramolecular Diels–Alder cycloaddition followed by an oxidative rupture of the connective unit as the key step, the unusual carbon framework of (−)-myltaylenol was established.

In 1985 Matsuo[1] and his colleagues reported the isolation of the unusual sesquiterpenoid alcohol (−)-myltaylenol **1** from the liverwort *Mylia taylorii*. The compound is characterized by a novel polycyclic terpenoid framework containing three consecutive quartenary carbon atoms and although Srikrishna[2] and his group in 1994 briefly described a remarkable biomimetic transformation, which finally gave rise to the corresponding racemic desoxy compound starting from cyclogeraniol, no enantioselective approach to this type of molecule has been reported.

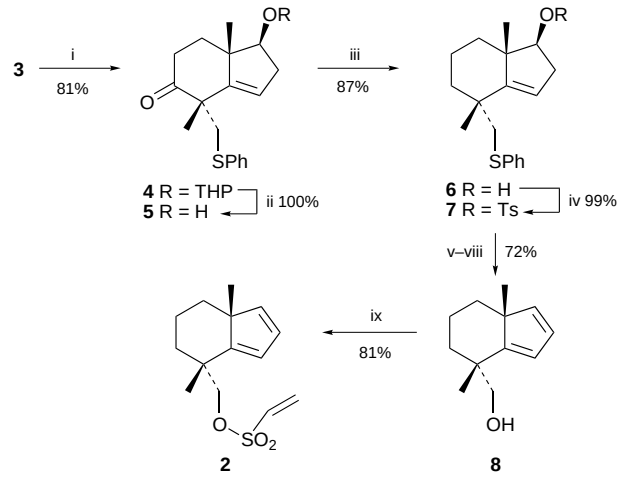
As retrosynthetic planning disclosed an intramolecular Diels–Alder cycloaddition employing cyclopentadiene **2** to be a potential key step and since we had in recent years gained some experience with dienes of this type, the enantioselective preparation of this compound was considered our first target.

For hydrindane derivatives of this structure the pure enantiomers of the Hajos–Wiechert ketone had been shown in our group to be an ideal starting material[3] and as the monoalkylated derivative **3** is well described in the literature[4] we employed the highly selective alkylation of this unsaturated ketone with thiophenylmethyl iodide followed by a Wolff–Kishner reduction to prepare the cyclopentenol **5**. To generate the corresponding cyclopentadiene, the tosylate **7** was formed and treated with potassium *tert*-butoxide in THF at 65 °C. Subsequent Pummerer rearrangement followed by a borohydride reduction gave rise to the primary alcohol **8**, which after treatment with ethenesulfonyl chloride was ready for the intramolecular cycloaddition. For this process and the accompanying oxidative ring fission of the sulfonate we had decided on the Metz protocol.[5] This worked nicely as far as the intramolecular cycloaddition was concerned. The oxidation employing 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, however, which had been successfully applied by Metz and his colleagues in various instances, failed. Since the electrophilic attack has to take place next to a quarternary carbon atom we came to the conclusion that steric hindrance may be the cause for this failure. We thus treated the carbanion of **9**, generated using Bu^{s}Li, with molecular oxygen and were pleased to note the clear formation of hydroxy ketone **10**. As the yield under various conditions, however, barely exceeded 40% we investigated the relationship between the amount of Bu^{s}Li used and the yield under standard reaction conditions and noticed that a large surplus of the deprotonating species (10–11 equiv.) reliably gave a 65% yield of the hydroxy ketone. With this piece of information at hand one may speculate about the formation of *sec*-butyl hydroperoxide and its possible role as an oxidant. We hesitate, however, to discuss the mechanism of this useful process at this stage of our investigation.

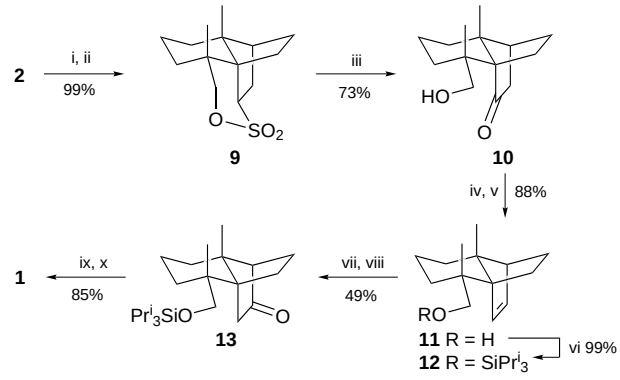
Without collecting further information about this oxidation we converted the keto group into the corresponding olefin **11** in a Shapiro reaction. Since it was hoped that a very bulky protecting group on the primary alcohol would change it into a large inert moiety, thus rendering the subsequent borane addition/oxidation sequence highly regioselective, triisopropylsilyl triflate in the presence of triethylamine was used as



Scheme 1



Scheme 2 *Reagents and conditions*: i, KOBu^t, THF, 0 °C, then $PhSCH_2I$, THF, −78 °C, 30 min; ii, HCl·EtOH, room temp., 16 h; iii, KOH, N_2H_4, diglycol, 200 °C, 4 h; iv, TsCl, DMAP, CH_2Cl_2, room temp., 16 h; v, KOBu^t, THF, 65 °C, 3.5 h; vi, $NaIO_4$, MeOH, 0 °C → room temp., 16 h; vii, Ac_2O, 100 °C, 62 h; viii, KOH, MeOH, room temp., 2 h, then $NaBH_4$, 0 °C, 30 min; ix, $ClSO_2CH{=}CH_2$, $EtNPr^i_2$, CH_2Cl_2, −15 °C, 1.5 h



Scheme 3 *Reagents and conditions*: i, toluene, 111 °C, 20 h; ii, Pd/C, H_2, THF, room temp., 16 h; iii, Bu^{s}Li, O_2, THF–HMPA (7 : 1), −78 °C, 3 h; iv, TsN_2H_3, TsOH, EtOH, MS 3 Å, 78 °C, 2 h; v, BuLi, THF, 75 °C, 50 min; vi, Pr^i_3SiOTf, NEt_3, THF, −78 °C, 2 h; vii, BH_3·THF, THF, 0 °C, 24 h, then NaOH, H_2O_2, EtOH, 50 °C, 3 h; viii, DMSO, $(COCl)_2$,NEt_3, CH_2Cl_2, −60 °C; ix, Ph_3PMeBr, KOBu^t, benzene, room temp., 48 h; x, Bu_4NF, THF, room temp., 18 h

the silylating reagent. Although models indicate a remarkable regional shielding of the cyclopentene **12** the observed selectivity was less than 1.5 : 1 in favour of the desired ketone **13**.

As the chromatographic separation of the intermediate pairs of epimeric secondary alcohols did not pose any problems and the subsequent Swern oxidation gave a high yield of the corresponding ketone, we were at this stage ready to use a Wittig reaction for the introduction of the exocyclic double bond. This operation as well as the subsequent deprotection with tetrabutylammonium fluoride proceeded in very high yield and gave rise to (−)-myltaylenol **1**, which by comparison with authentic spectra kindly provided by Dr Matsuo proved to be the desired natural compound.

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Footnote and References

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