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A Flexible, Stereoselective Approach to the Decorated *cis*-Hydrindane Skeleton: Synthesis of the Proposed Structure of Faurinone

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Since its introduction to the synthetic community by Kagan, the one-electron reducing agent samarium(II) iodide (SmI_2) has found widespread use in organic synthesis.[1] The reagent has been used to mediate many processes ranging from functional group interconversions to complex carbon-carbon bond-forming sequences.[1] Cyclisation reactions are among the most useful transformations mediated by SmI_2 and these have proved to be valuable tools for natural product synthesis.[1k] The intramolecular addition of radicals, generated from aldehydes and halides, to alkenes, are among the most common classes of cyclisation mediated by the reagent.[1]

The hydrindane skeleton is found in a multitude of biologically active natural products. We wished to develop a stereoselective approach to the *cis*-hydrindane skeleton **1** that would allow stereocontrolled installation of substituents around the bicyclic structure.[2] A flexible approach to **1** would facilitate approaches to a number of natural products, many of which display important biological activity (Figure 1). The sesquiterpene glycosides, dendronobiloside A and B, display immunomodulatory activity,[3] and are closely related to faurinone **2**.[4] Pleuromutilin **3** has an inhibitory effect against the bacteria *Staphylococcus aureous* and is known to prevent bacterial protein synthesis.[5] Bakkenolides, such as **4**, display a variety of biological activities including selective cytotoxicity.[6] Here we report a flexible approach to the substituted *cis*-hydrindane skeleton that exploits diastereoselective conjugate additions to β-substituted cyclohexenones in conjunction with highly diastereoselective SmI_2-mediated cyclisations of aldehyde and halide substrates. We have applied the approach in the first synthesis of the proposed structure of *rac*-faurinone.

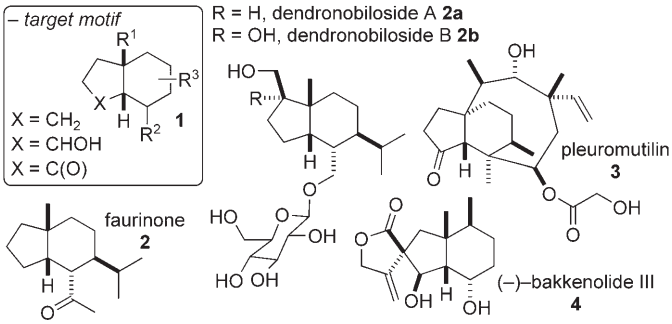
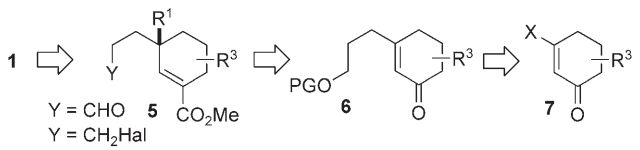


Figure 1. Selected natural products containing a substituted *cis*-hydrindane core.

We envisaged constructing the quaternary stereocentre in **1** by conjugate addition to substituted β-alkyl cyclohexenones. Prior to our work, little was known about the efficacy and diastereoselectivity of such additions.[7] Aldehydes or halides **5** would therefore be accessible from enones **7** via intermediates **6**. We believed that substrates **5** would undergo highly stereoselective cyclisations on treatment with SmI_2. The flexible approach would provide expedient access to the cores of a number of natural products (Scheme 1).

Aldehydes **13** and **14** were prepared to investigate the diastereoselectivity of the proposed SmI_2-mediated construction of the *cis*-hydrindane system. Grignard addition to **8**[8] according to the procedure of Tietze et al.,[9] and protection



Scheme 1. General approach to the *cis*-hydrindane skeleton (PG = protecting group, X = H or OEt).

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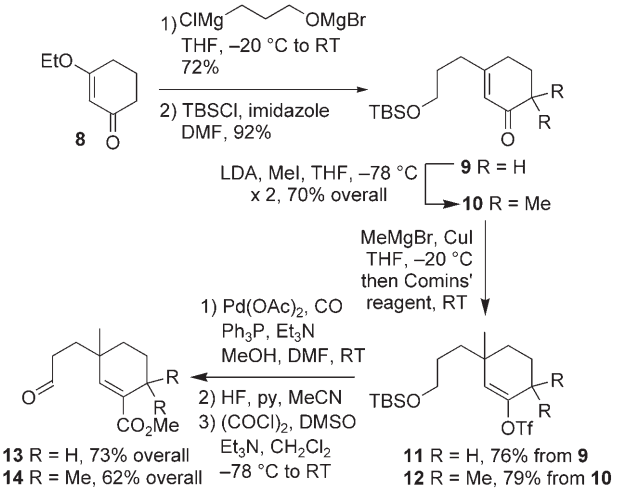
of the primary hydroxy group gave **9** (Scheme 2). Subsequent dimethylation of enone **9** gave **10**. Treatment of enones **9** and **10** with dimethylcuprate and trapping of the resultant enolates with Comins' reagent[10] gave enol triflates



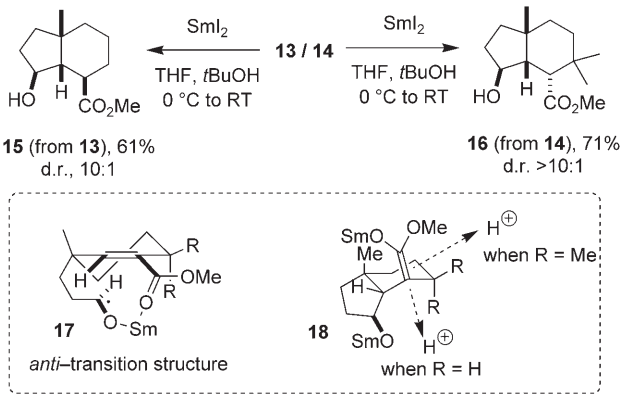
Scheme 2. General route to cyclisation substrates (Comins' reagent = *N*-(5-chloro-2-pyridyl)triflimide).

11 and **12**, respectively. Palladium-catalysed methoxycarbonylation, deprotection, and oxidation then gave **13** and **14** in excellent overall yield (Scheme 2).

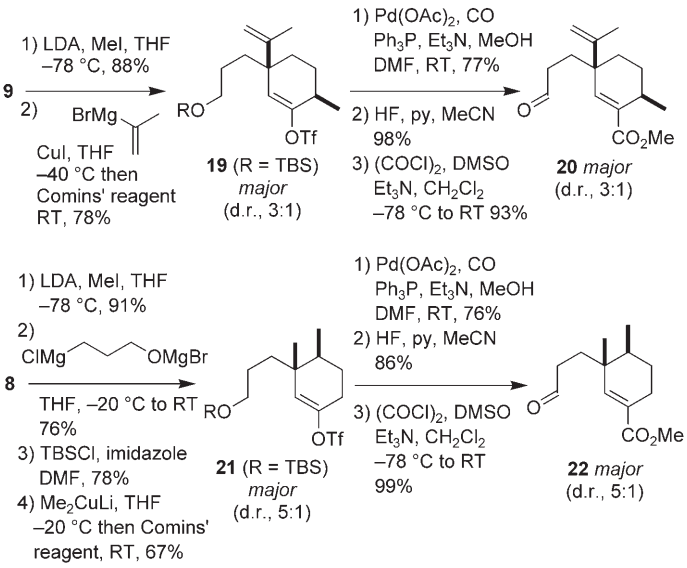
Pleasingly, treatment of **13** and **14** with SmI_2 in THF and *t*BuOH resulted in successful cyclisation and concomitant construction of three contiguous stereocentres. Products **15** and **16** were obtained in high yield and with high diastereoselectivity (d.r., >10:1 by ^{1}H NMR spectroscopy, α- to the ester). Strikingly, **13** underwent cyclisation to give **15** as the *syn*, *syn*-diastereoisomer, whereas cyclisation of **14** gave **16** as the *syn, anti*-diastereoisomer. The stereochemistry of the products was confirmed by conversion of **15** and **16** to the corresponding 1-naphthyl carbamates and subsequent X-ray crystallographic analysis.[11] The SmI_2-mediated cyclisation proceeds via reduction of the aldehyde and addition of the resulting ketyl-radical anion to the alkene through *anti*-transition structure **17** to give samarium(III) enolates **18**.[12]

Protonation of the enolate in these systems typically occurs selectively from the α-face (vide infra). In the cyclisation of **13** (R = H), α-protonation occurs to give **15**, however, reaction of **14** (R = Me) gives rise to a samarium(III) enolate in which protonation from the α-face is blocked by an axial methyl group, and quenching from the β-face occurs to give **16** (Scheme 3).

The general route can be adapted to access *cis*-hydrindane frameworks decorated with five stereocentres (Schemes 4 and 5). The formation of enol triflate **19** illustrates the utility of the cuprate addition for the stereocontrolled construction of the quaternary stereocentre and the introduction of groups other than methyl. Enol triflate **21** was prepared by methylation of enol ether **8**, Grignard addition, protection, and methylcuprate addition–enolate trapping. Enol triflates



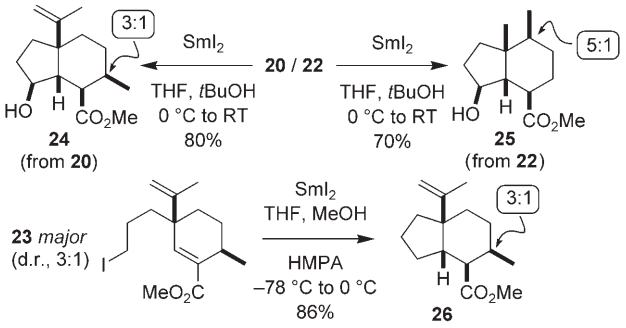
Scheme 3. Diastereoselective samarium(II)-mediated cyclisations.



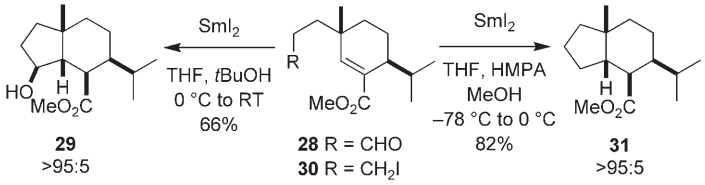
Scheme 4. Diastereoselective route to cyclisation substrates.

19 and **21** were then converted to cyclisation substrates **20** and **22** using the straightforward sequence outlined in Scheme 2.

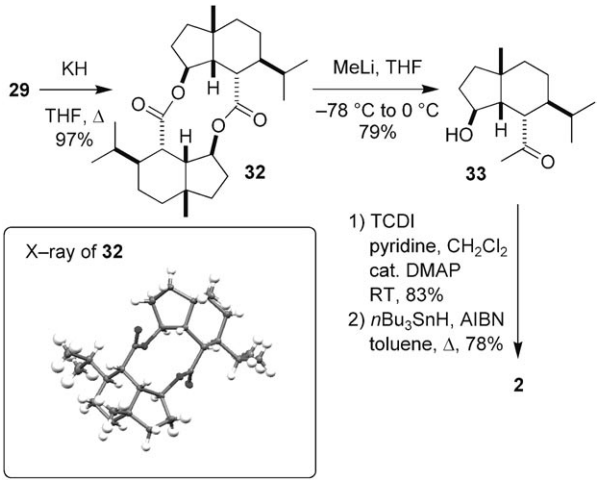
An alkyl iodide cyclisation substrate **23** was also prepared from an intermediate, protected alcohol in three steps (HF, pyridine, MeCN; MsCl, NEt_3, CH_2Cl_2; NaI, acetone; 74% over 3 steps). Treatment of **20** and **22** with SmI_2 in THF and *t*BuOH resulted in successful cyclisation, and products **24** and **25** were obtained in high yield with excellent diastereocontrol, again being observed in the cyclisation (d.r., >10:1 by ^{1}H NMR spectroscopy). The stereochemistry of **24** was confirmed by X-ray crystallography on a related product,[11] while the stereochemistry of **25** was confirmed by NOE studies. Iodide **23** also underwent highly diastereoselective cyclisation (d.r., >5:1 by ^{1}H NMR spectroscopy) on treatment with SmI_2-HMPA[13] to give **26**. SmI_2-mediated halide-alkene cyclisations provide a convenient alternative for the synthesis of less-oxygenated targets (Scheme 5). Cyclisation products **24** and **25** possess the substitution patterns found



Scheme 5. Diastereoselective samarium(II)-mediated cyclisations.



Scheme 7. Diastereoselective samarium(II)-mediated cyclisations in an approach to the proposed structure of faurinone.

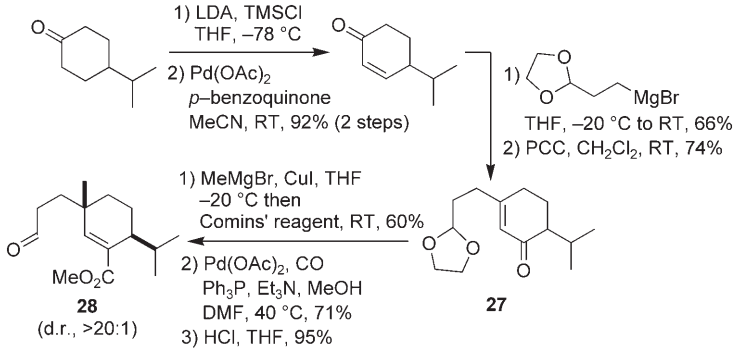


Scheme 8. Completing an approach to the proposed structure of faurinone (TCDI = 1,1′-thiocarbonyldiimidazole).

in the *cis*-hydrindane cores of pleuromutilin **3** and bakkenolide III **4**, respectively (see Figure 1)

We have exploited the approach in a concise synthesis of the proposed structure of faurinone (**2**), a sesquiterpene ketone isolated from *Valeriana officinalis* (Figure 1).[4] The TMS enol ether derived from 4-isopropylcyclohexanone underwent Saegusa oxidation[14] to give 4-isopropylcyclohexenone.[15] Grignard addition and oxidative rearrangement of the resultant tertiary alcohol with pyridinium chlorochromate (PCC) then gave enone **27**. Highly diastereoselective organocopper addition, enolate trapping, carbonylation and acetal deprotection gave cyclisation substrate **28** (d.r., >20:1) (Scheme 6).

As expected, cyclisation of aldehyde **28** with SmI_2 proceeded with excellent stereocontrol to give **29** as a single



Scheme 6. Preparation of the cyclisation substrate in an approach to the proposed structure of faurinone.

diastereoisomer by ^{1}H NMR spectroscopy. The stereochemical outcome of the cyclisation was confirmed by conversion of **29** to the corresponding 1-naphthyl carbamate and X-ray crystallographic analysis.[11] Alkyl iodide **30** was prepared from **28** ($NaBH_4$, THF-MeOH, RT, then I_2, Ph_3P, imidazole, CH_2Cl_2, RT; 58% for two steps) and underwent smooth cyclisation on treatment with SmI_2-HMPA[13] to give **31** as a single diastereoisomer by ^{1}H NMR spectroscopy (Scheme 7).

Our approach to faurinone continued with the epimerisation of **29** and formation of the bis-lactone **32**. The structure of **32** was confirmed by X-ray crystallography.[11] Reaction of **32** with methyllithium gave **33** in good yield. We believe the stability of the cyclic, bis-hemi-ketal accounts for the smooth monoaddition of methyllithium to each carbonyl group. Conversion of **33** to the thioimidazolide and radical deoxygenation completes the first synthesis of the proposed structure of faurinone **2**[16] (Scheme 8).

We have developed a flexible, stereoselective approach[17] to the *cis*-hydrindane motif found in a number of biologically active natural products that utilizes highly diastereoselective SmI_2-mediated cyclisations of aldehyde and halide substrates. The strategy has been exploited in the first synthesis of the proposed structure of faurinone, a sesquiterpene ketone isolated from *Valeriana officinalis*.

Acknowledgements

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[16] The structure originally proposed for faurinone by Hikino et al. was revised by Bos et al. (see ref. [4]). While only partial spectroscopic data is available for the natural product, NMR data for synthetic **2** prepared during our studies does not match the partial, reported data in ref. [4]. We have also prepared *epi*-**2** from **31** ($TMSCH_2Li$, THF, 0°C, 77%). *epi*-**2** also does not match the partial reported data given in ref. [4].

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