

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 aureus* 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

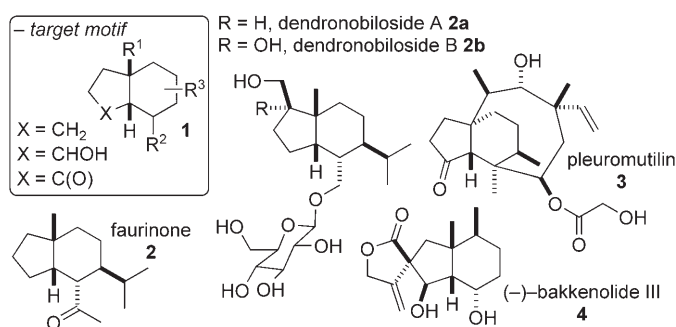
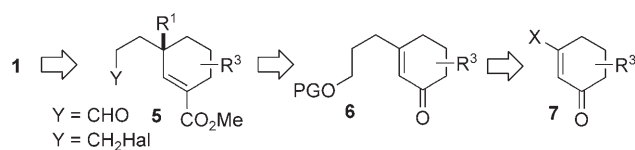


Figure 1. Selected natural products containing a substituted *cis*-hydrindane core.

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.

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



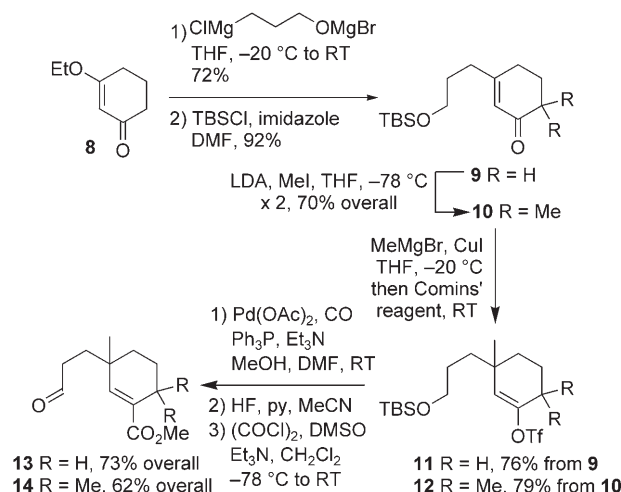
Scheme 1. General approach to the *cis*-hydrindane skeleton (PG = protecting group, X = H or OEt).

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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



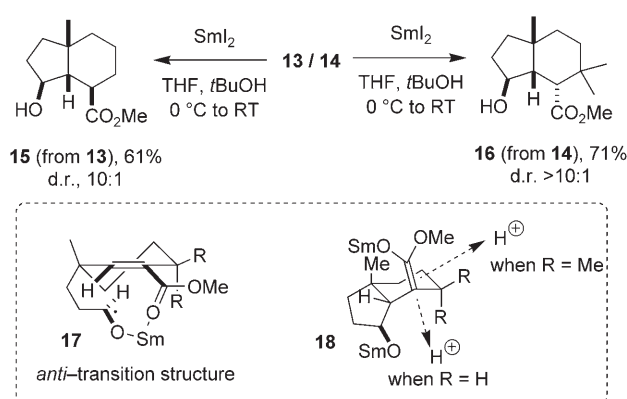
Scheme 2. General route to cyclisation substrates (Comins' reagent = *N*-(5-chloro-2-pyridyl)triflimide).

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

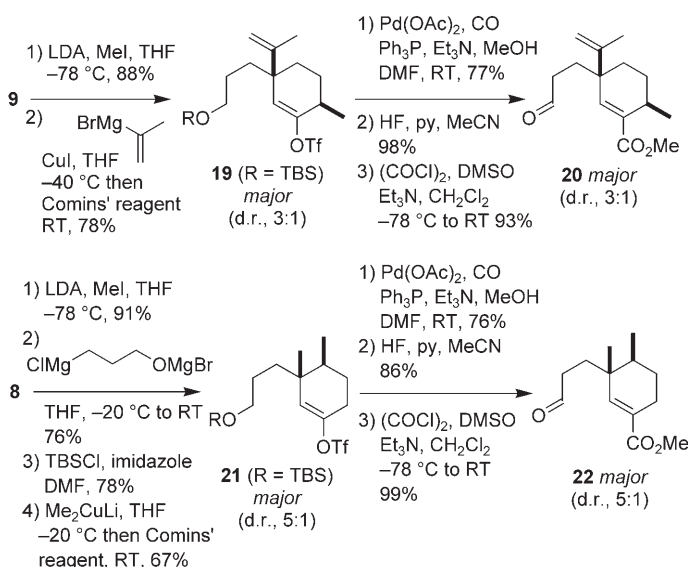
Pleasingly, treatment of **13** and **14** with SmI_2 in THF and *t*BuOH resulted in successful cyclisation and concomitant construction of three contiguous stereocentres. Products **15** and **16** were obtained in high yield and with high diastereoselectivity (d.r., >10:1 by ^1H NMR spectroscopy, α - 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



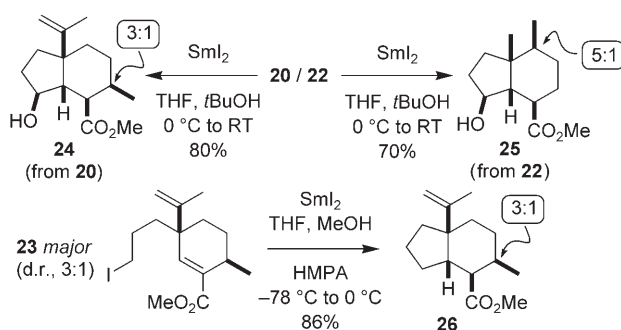
Scheme 3. Diastereoselective samarium(II)-mediated cyclisations.



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 ^1H 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 ^1H 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

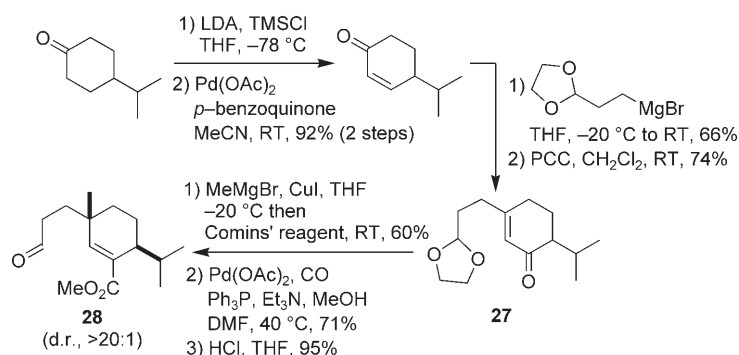


Scheme 5. Diastereoselective samarium(II)-mediated cyclisations.

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 faurinine (**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).

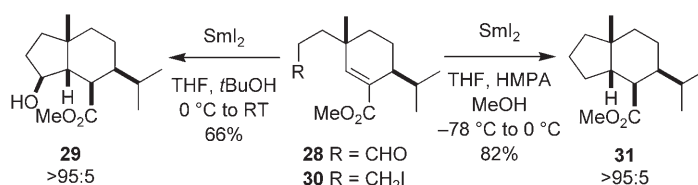
As expected, cyclisation of aldehyde **28** with SmI_2 proceeded with excellent stereocontrol to give **29** as a single



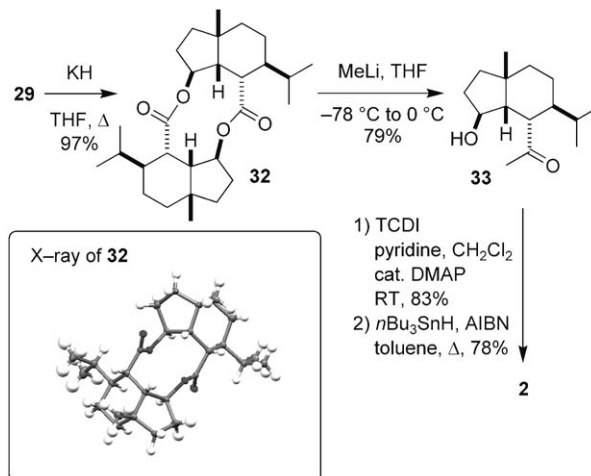
Scheme 6. Preparation of the cyclisation substrate in an approach to the proposed structure of faurinine.

diastereoisomer by ^1H 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 ^1H NMR spectroscopy (Scheme 7).

Our approach to faurinine 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



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



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

the stability of the cyclic, bis-hemi-ketal accounts for the smooth monoaddition of methyllithium to each carbonyl group. Conversion of **33** to the thioimidazolidine and radical deoxygenation completes the first synthesis of the proposed structure of faurinine **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 faurinine, a sesquiterpene ketone isolated from *Valeriana officinalis*.

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- [1] For a review of metal-mediated radical reactions, see: a) A. Gansauer, H. Bluhm, *Chem. Rev.* **2000**, *100*, 2771. For reviews on the use of SmI₂ in organic synthesis, see: b) G. A. Molander, *Chem. Rev.* **1992**, *92*, 29; c) G. A. Molander, *Org. React.* **1994**, *46*, 211; d) G. A. Molander, C. R. Harris, *Chem. Rev.* **1996**, *96*, 307; e) T. Skrydstrup, *Angew. Chem.* **1997**, *109*, 355; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 345; f) G. A. Molander, C. R. Harris, *Tetrahedron* **1998**, *54*, 3321; g) H. Kagan, J. L. Namy, *Lanthanides: Chemistry and Use in Organic Synthesis* (Ed.: S. Kobayashi), Springer, **1999**, p. 155; h) A. Krief, A.-M. Laval, *Chem. Rev.* **1999**, *99*, 745; i) P. G. Steel, *J. Chem. Soc. Perkin Trans. 1* **2001**, 2727; j) H. B. Kagan, *Tetrahedron* **2003**, *59*, 10351; k) D. J. Edmonds, D. Johnston, D. J. Procter, *Chem. Rev.* **2004**, *104*, 3371; l) A. Dahlén, G. Hilmersson, *Eur. J. Inorg. Chem.* **2004**, 3393.
- [2] For selected, recent approaches to the hydrindane skeleton, see: a) T. Kusakabe, K. Kato, S. Takaishi, S. Yamamura, T. Mochida, H. Akita, T. A. Peganova, N. V. Vologdin, O. V. Gusev, *Tetrahedron* **2008**, *64*, 319; b) A.-S. Chapelon, C. Ollivier, M. Santelli, *Tetrahedron Lett.* **2006**, *47*, 2747; c) G. Pandey, S. B. Raikar, *Tetrahedron Lett.* **2006**, *47*, 2029; d) R. Rodriguez, C. Ollivier, M. Santelli, *Synlett* **2006**, 312; e) Y. Nakai, Y. Uozumi, *Org. Lett.* **2005**, *7*, 291; f) H. Araki, M. Inoue, T. Katoh, *Synlett* **2003**, 2401; g) I. Prowotorow, W. Stepanenko, J. Wicha, *Eur. J. Org. Chem.* **2002**, 2727; h) G. Mehta, K. Islam, *Angew. Chem.* **2002**, *114*, 2502; *Angew. Chem. Int. Ed.* **2002**, *41*, 2396; i) D. N. Jones, M. W. J. Maybury, S. Swallow, N. C. O. Tomkinson, W. W. Wood, *Tetrahedron Lett.* **2001**, *42*, 2193.
- [3] W. Zhao, Q. Ye, X. Tan, H. Jiang, X. Li, K. Chen, A. D. Kinghorn, *J. Nat. Prod.* **2001**, *64*, 1196.
- [4] a) H. Hikino, Y. Hikino, K. Agatsuma, T. Takemoto, *Chem. Pharm. Bull.* **1968**, *16*, 1779; b) R. Bos, H. Hendriks, J. Kloosterman, G. Sipma, *Phytochemistry* **1983**, *22*, 1505.
- [5] a) F. Kavanagh, A. Herve, W. J. Robbins, *Proc. Natl. Acad. Sci. USA* **1951**, *37*, 570; b) S. M. Poulsen, M. Karlsson, L. B. Johansson, B. Vester, *Mol. Microbiol.* **2001**, *41*, 5, 1091; c) F. Schlünzen, E. Pyetan, P. Fucini, A. Yonath, J. M. Harms, *Mol. Microbiol.* **2004**, *54*, 5, 1287.
- [6] a) N. Abe, R. Onoda, K. Shirahata, T. Kato, M. C. Woods, Y. Kitahara, K. Ro, T. Kurihara, *Tetrahedron Lett.* **1968**, *9*, 1993; b) T. J. Brocksom, F. Coelho, J.-P. Deprés, A. E. Greene, M. E. Freire de Lima, O. Hamelin, B. Hartmann, A. M. Kanazawa, Y. Wang, *J. Am. Chem. Soc.* **2002**, *124*, 15313.
- [7] a) A. Solladié-Cavallo, L. Jierry, L. Bouérat, P. Taillisson, *Tetrahedron: Asymmetry* **2001**, *12*, 883; b) L. Mediavilla Urbaneja, A. Alexakis, N. Krause, *Tetrahedron Lett.* **2002**, *43*, 7887.
- [8] W. F. Gannon, H. O. House, *Org. Synth.* **1973**, *5*, 539.
- [9] L. F. Tietze, H. Schirok, M. Wöhrmann, *Chem. Eur. J.* **2000**, *6*, 510.
- [10] D. L. Comins, A. Dehghani, *Tetrahedron Lett.* **1992**, *33*, 6299.
- [11] CCDC-684740, CCDC-684741, CCDC-684742, CCDC-684744 and CCDC-684745 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Further information is available in the Supporting Information.
- [12] For a review on Sm enolates, see: I. M. Rudkin, L. C. Miller, D. J. Procter, *Organomet. Chem.* **2008**, *34*, 19.
- [13] S. M. Bennett, R. K. Biboutou, Z. Zhou, R. Pion, *Tetrahedron* **1998**, *54*, 4761.
- [14] Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011.
- [15] 4-Isopropylcyclohexenone could also be prepared in 94% yield from nopinone using the procedure of Mori: K. Mori, *Tetrahedron: Asymmetry* **2006**, *17*, 2133.
- [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** (TMSCH₂Li, THF, 0°C, 77%). *epi-2* also does not match the partial reported data given in ref. [4].
- [17] Access to enantiomerically-enriched 4-alkylcyclohexenones, using the approach of Koga et al., allows the asymmetric synthesis of *cis*-hydrindanes using our approach. K. Aoki, M. Nakajima, K. Tomioaka, K. Koga, *Chem. Pharm. Bull.* **1993**, *41*, 994.

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