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Studies in Marine Macrolide Synthesis: Boron and Silicon-Mediated Coupling Strategies for Swinholide A.

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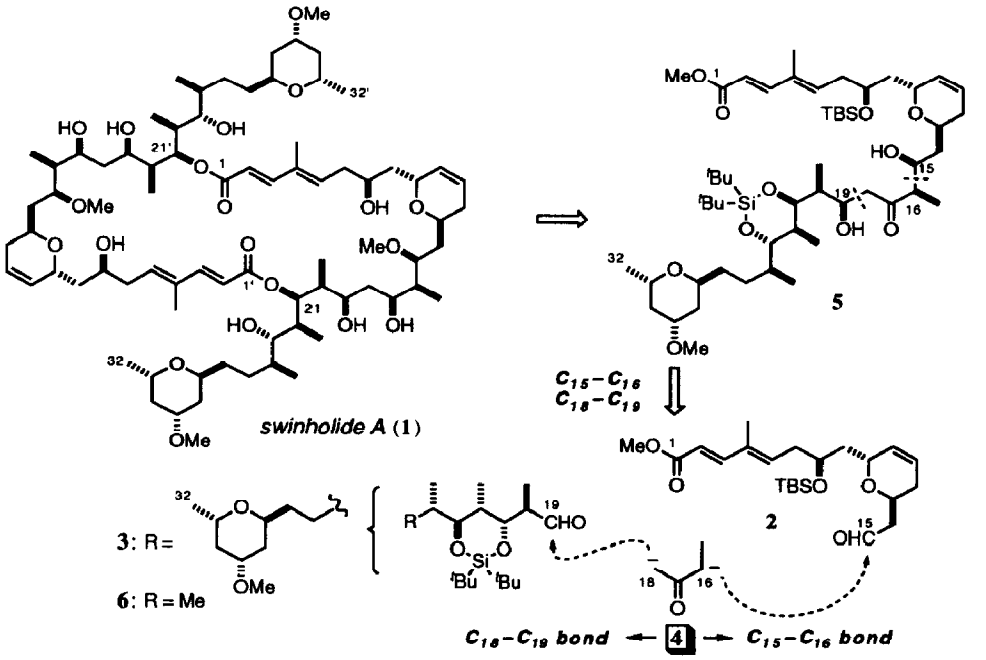
Abstract: Reaction of aldehyde **6** with enol borinates **7** gives adduct **10** preferentially, whereas the allylsilane **18** provides the epimeric adduct **11** with 95% ds. Aldehyde **2** reacts mainly by *si*-face attack with simple *Z* enol borinates, which can be overturned by reagent control from (+)-**25**.

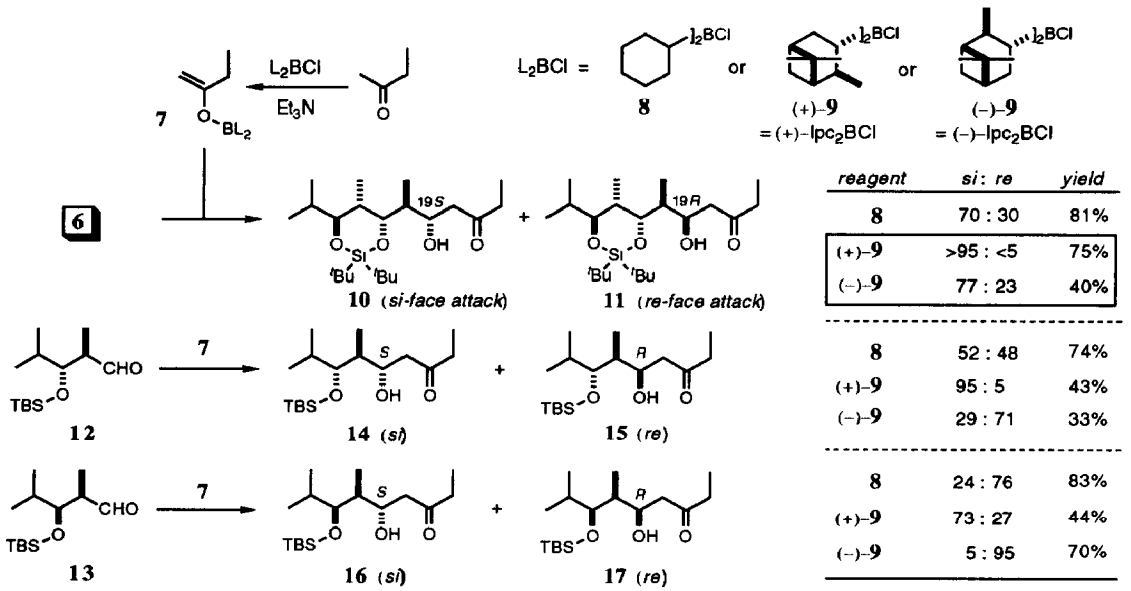
Swinholide A (**1**), isolated from the marine sponge *Theonella swinhoei*, is a 44-membered dimeric macrodiolide having potent cytotoxic activity.[1] As part of our efforts directed towards the total synthesis of swinholide A[2a-c] and related marine macrolides,[2d] we recently reported the preparation of the two aldehydes **2**[2c] and **3**[2a] as C_1–C_{15} and C_{19}–C_{32} subunits, respectively. As shown in **Scheme 1**, our synthetic plan next requires the controlled coupling of these chiral aldehydes with a suitable butanone synthon **4** to lead to the secoacid derivative **5**, correctly incorporating the three stereocentres at C_{15}, C_{16} and C_{19}.



Scheme 1

We now report the results of some model studies for the construction of the swinholide C_{18}–C_{19} and C_{15}–C_{16} bonds employing both single and double[3] asymmetric induction strategies. Selective *re*- or *si*-face attack on aldehyde **6** was found to be possible by suitable choice of boron or silicon reagent, whereas aldehyde **2** showed an intrinsic diastereofacial preference for undesired *si*-face attack with simple boron enolates. For both these coupling situations, together with some related cases, the scope and limitations of reagent control using enol diisopinocampheylborinates[4] was explored.

C_{18}–C_{19} Bond Formation. As shown in **Scheme 2**, we initially examined the aldol addition of the enol borinates **7** to the aldehyde **6**, which was chosen as a model[5] for the complete C_{19}–C_{32} subunit **3**. Following the protocol of Brown *et al.*,[6] kinetic enolisation of butanone was performed in Et_2O with each of the chloroboranes **8**, (+)-**9**, and (–)-**9**. In the presence of Et_3N, complete regiocontrol in the enolisation of butanone to the methyl side is obtained.[7] The derived enol borinates **7** were then added to **6** to generate the epimeric adducts **10** and **11**.[8] Using the achiral reagent **8**, a 70 : 30 ratio of the two epimers was obtained in favour of **10** by undesired *si*-face attack. The chiral reagent (+)-**9** gave a high level of selectivity for **10** (≥95% ds), as expected[4] for a matched reaction. Surprisingly, the enantiomeric reagent (–)-**9** also gave **10** with improved selectivity (77% ds). Hence, reagent control failed to provide the required syn isomer **11**.



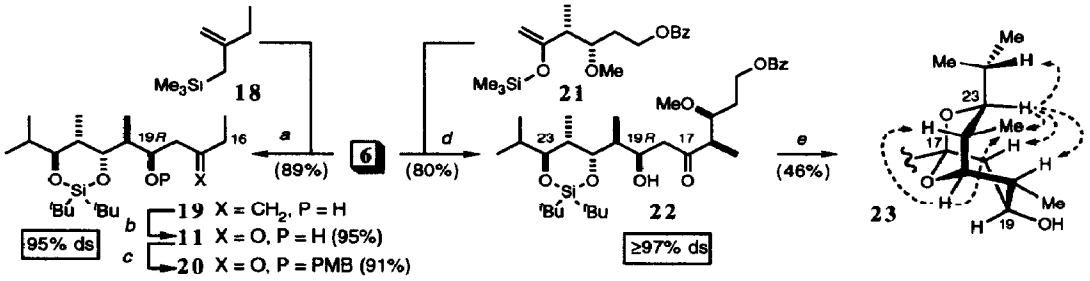
reagent	si : re	yield
8	70 : 30	81%
(+)-**9**	>95 : <5	75%
(–)-**9**	77 : 23	40%
8	52 : 48	74%
(+)-**9**	95 : 5	43%
(–)-**9**	29 : 71	33%
8	24 : 76	83%
(+)-**9**	73 : 27	44%
(–)-**9**	5 : 95	70%

Scheme 2 *Aldol conditions:* L_2BCl, Et_3N, Et_2O, 0 °C, 30 min (→ **7**); aldehyde (**6**, **12**, or **13**), –78 → –25 °C, 18 h; H_2O_2, MeOH–pH7 buffer.

In order to investigate this situation further, the structurally-related aldehydes[9] **12** and **13** were submitted to the same aldol reactions. Using the achiral reagent **8**, aldehyde **12** gave equal amounts of **14** and **15**, while the β-epimeric aldehyde **13** gave **16** and **17** with moderate selectivity (76% ds) for the latter isomer.[10] Here, (+)-**9** led to *si*-face selectivity towards **14** and **16**, while (–)-**9** favoured **15** and **17** by *re*-face attack. These results are qualitatively as expected,[3] with high stereoselectivities (95% ds) in the matched combinations and moderate stereoselectivities (71-73% ds) in the other sense for the mismatched cases. *Thus, it appears that the Ipc-mediated additions to aldehyde* **6** *are anomalous, since the substrate-induced si-face selectivity is enhanced for both enantiomers of the reagent.* There is clearly a significant contribution from the aldehyde structure (including the β-stereocentre), together with the steric demands and chirality of the ligands on boron in the enolate component, to the stereochemical result. Simple models for predicting asymmetric induction in methyl ketone boron aldol reactions with chiral aldehydes are unlikely to be reliable. The accessibility of chair and boat transition states adds to the uncertainty.[4,11]

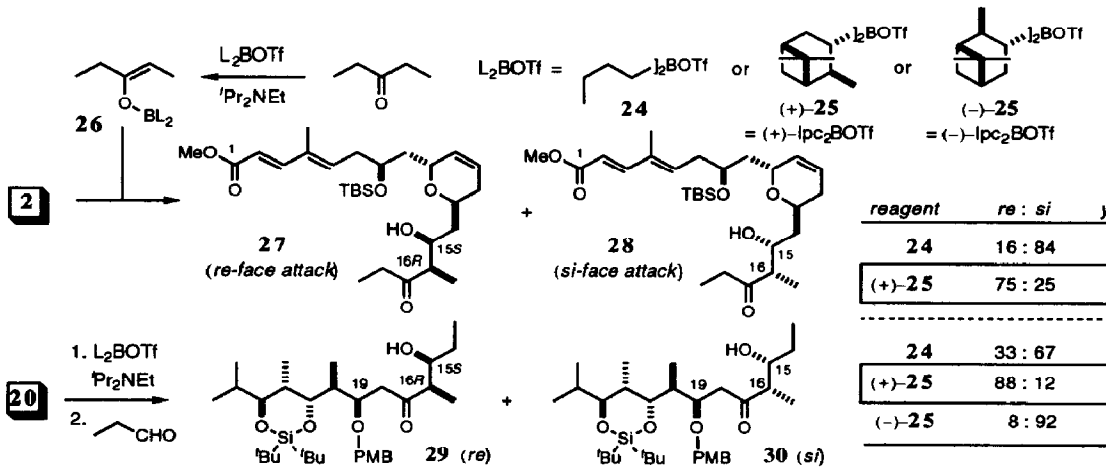
In the light of the above findings, a different strategy was required for C_{18}–C_{19} bond formation. We next turned to the use of the allylsilane[12] **18** (**Scheme 3**), as a masked butanone enolate equivalent, requiring Felkin-Anh selectivity in its Lewis acid-mediated addition to **6**. In practice, the use of $TiCl_4$ (1 equiv, CH_2Cl_2, -78 °C) provided the required (19*R*)-adduct **19** with 95% ds in 89% yield, which was converted into ketone **11** by ozonolysis.[8] Hydroxyl protection gave the *p*-methoxybenzyl (PMB) ether derivative **20** for subsequent study

of syn aldol additions at C_{16}. Encouraged by the allylsilane result, a Mukaiyama aldol addition of a model silyl enol ether was also explored. Using $BF_3{\cdot}OEt_2$ as the Lewis acid, the silyl enol ether **21** was added to aldehyde **6** to give ketone **22**, again having the required (19*R*)-configuration for swinholide A. The high selectivity (≥97% ds) and yield obtained in this model coupling reaction are notable.[13] After silylene deprotection, the stereochemistry was established by extensive NOE studies on the derived bicyclic acetal **23** and the corresponding acetals derived from **10** and **11**.[8]



Scheme 3 (*a*) $TiCl_4$, CH_2Cl_2, –78 °C, 5 min; (*b*) O_3, CH_2Cl_2/MeOH (3:1), –78 °C, 3 min; Me_2S, –78 → 20 °C, 18 h; (*c*) PMBOC(CCl$_3$)=NH, cat. TfOH, Et_2O, 20 °C, 40 min; (*d*) $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C, 30 min; (*e*) HF•pyridine, pyridine, THF, 20 °C, 15 min.

C_{15}–C_{16} Bond Formation. The π-facial selectivity of aldehyde **2** with *Z* enol borinates was explored to set up the correct syn aldol relationship at C_{15}–C_{16}. Using the triflate reagents **24** and (+)-**25**,[4] diethylketone was initially used as a simple model. As shown in **Scheme 4**, the aldol reaction of **2** with the achiral *Z* enol boronate **26** (L = ^{n}Bu)[14] gave the syn adducts **27** and **28**.[8] The major isomer **28**, formed with 84% ds, corresponded to that obtained by *si*-face attack, *i.e.* opposite to that required for swinholide A. This could be overturned using reagent control[4] employing (+)-**25** to give **27** as the major isomer with 75% ds.



Scheme 4 *Aldol conditions:* L_2BOTf, $^iPr_2NEt$, CH_2Cl_2, –78 °C, 2 h; aldehyde (**2** or EtCHO), –78 → –25 °C, 18 h; H_2O_2, MeOH–pH7 buffer.

We then investigated the π-facial bias arising from the chiral ketone component in this potential syn aldol coupling step. Enolisation of **20** with the simple triflate reagent **24** and addition of propionaldehyde gave the syn adducts **29** and **30**.[15] Again, the major isomer **30** corresponded to undesired *si*-face attack on the aldehyde component. Using reagent control from (+)-**25**, the required[15] isomer **29** was obtained with 88% ds, while the matched reagent (–)-**25** gave **30** with 92% ds. For a syn boron aldol coupling at C_{15}–C_{16}, the intrinsic diastereofacial selectivities of the two chiral components appear matched in the wrong stereochemical

sense. Hence, reagent control is required to correctly set up the (15*S*,16*R*) relationship for swinholide A.

In summary, these C_{18}–C_{19} coupling studies indicate that allylsilane or silyl enol ether additions to **6** provide the correct stereochemistry for swinholide A. If enol borinates are used, the epimeric adduct is formed instead. The high stereoselectivity (corresponding to the anti-Felkin sense) obtained using enol diisopinocampheylborinates, *i.e.* **6** → **10** and **12** → **14**, may prove valuable in other situations.[4] In contrast, the C_{15}–C_{16} syn aldol coupling is more of a problem. It appears to be matched in the undesired sense and thus requires a high level of reagent-based chiral influence to attain the swinholide stereochemistry. Further studies directed towards the total synthesis of swinholide A using these coupling strategies are underway.

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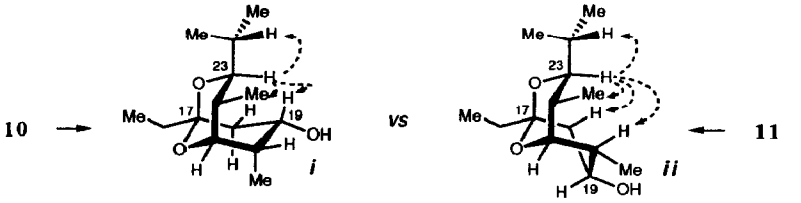
5. Aldehyde **6** was prepared in 5 steps from (*S*)-4-methyl-5-benzyloxypentan-3-one and isobutyraldehyde using a similar sequence to that employed in the synthesis of the C_{19}–C_{32} subunit **3** (see ref. 2a).
6. Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499.
7. For a rationalisation for this enolisation selectivity, see: Goodman, J. M.; Paterson, I. *Tetrahedron Lett.* **1992**, *33*, 7223.
8. All new compounds gave spectroscopic data in agreement with the assigned structures. The stereostructures of aldol adducts **10** and **11** were determined by conversion into the bicyclic acetals *i* and *ii* (HF•pyridine), followed by NOE studies:



9. The aldehydes **12** and **13** were prepared from the corresponding primary alcohols by Swern oxidation and used immediately.
10. The configurations at the new hydroxyl-bearing stereocentre in aldol adducts **14**–**17** and **28** were determined by ^{1}H NMR analysis of the derived (*R*)- and (*S*)-MTPA esters. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
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12. The allylsilane **18** was prepared from ethyl propionate by the method of Narayanan and Bunnelle, see: Narayanan, B. A.; Bunnelle, W. H. *Tetrahedron Lett.* **1987**, *28*, 6261.
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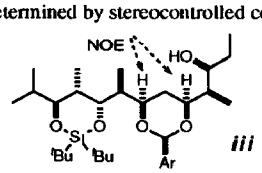
14. Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.
15. The stereochemistry of aldol adduct **29** was determined by stereocontrolled conversion into the benzylidene acetal *iii*.



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