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Total synthesis of altohyrtin A (spongistatin 1): an alternative synthesis of the CD-spiroacetal subunit

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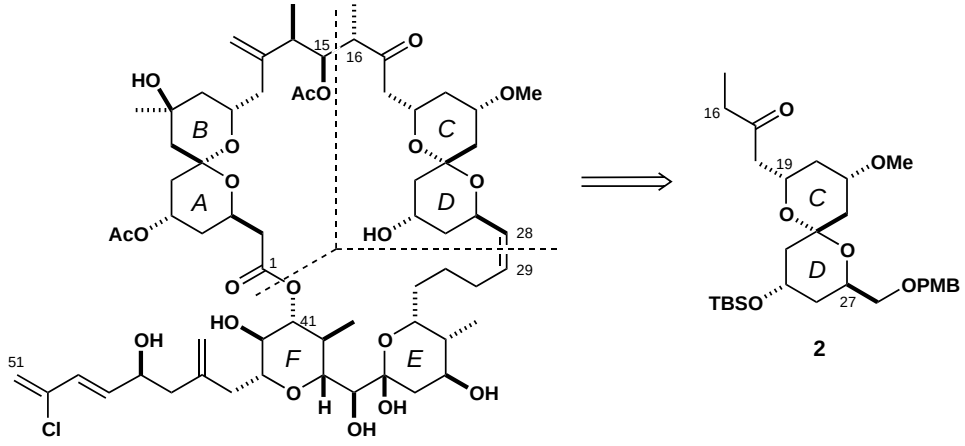
Abstract—The CD-spiroacetal containing C_{16}–C_{28} subunit **2**, as used in the total synthesis of the potent cytotoxic macrolide, altohyrtin A (spongistatin 1), was prepared by an alternative route using substrate-based stereocontrol in the two aldol bond constructions generating the acyclic precursor **4**. © 2002 Published by Elsevier Science Ltd.

The altohyrtins/spongistatins comprise an important family of highly cytotoxic macrolides, isolated from marine sponges.[1,2] They display exceptional growth inhibitory activity against a wide range of drug-resistant cancer cell lines, functioning by interfering with tubulin polymerisation. Their complex, highly oxygenated structures (e.g. **1**, Scheme 1) and potent antimitotic action, combined with an extremely meagre natural supply, have provided a strong impetus for synthetic efforts. Total syntheses of altohyrtin C (spongistatin 2) have been achieved by the Evans group[3] and more recently by the Smith group.[4] The first total synthesis of the more active, chlorinated congener, altohyrtin A/spongistatin 1 (**1**) by Kishi et al.,[5] was recently followed by our completion of a highly stereocontrolled synthesis, leading to useful quantities for further preclinical development.[6] With a view to further refining our total synthesis, we now report a new synthesis of the CD-spiroacetal containing subunit **2** that exploits substrate-based aldol stereocontrol.

The CD-spiroacetal of the altohyrtins/spongistatins benefits from only a single anomeric effect, necessitating care in initially establishing the C23 acetal centre



1: altohyrtin A (spongistatin 1)

Scheme 1.

Keywords: altohyrtin; spongistatin; boron aldol; cytotoxic; remote stereoinduction.

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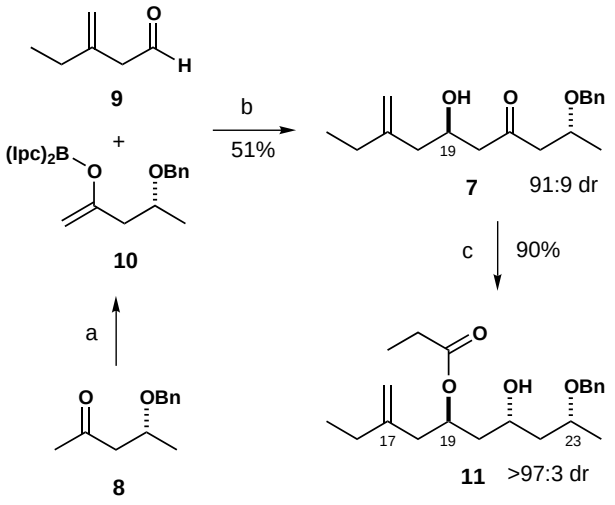
correctly and subsequently avoiding unwanted epimerisation.[7] Accordingly, our revised retrosynthetic analysis for **2** involved formation of the precursor **3a**, incorporating a C17-methylene, from ketone **4** by removal of the silyl protecting groups and concomitant spiroacetal formation (Scheme 2). The aldol coupling of ketone **5** with aldehyde **6** to give the required acyclic precursor **4** would depend on substrate-based stereoinduction in setting up the C25 stereocentre, as demonstrated in an analogous system.[6c] Ketone **5** would arise from **7** by 1,3-*anti* reduction and various functional group manipulations. The 1,5-*anti* relationship between the oxygen functionality in **7** suggested a boron-mediated aldol reaction[8] between the β-alkoxyketone **8** and β,γ-unsaturated aldehyde **9**, where substrate-based induction would again be employed productively.

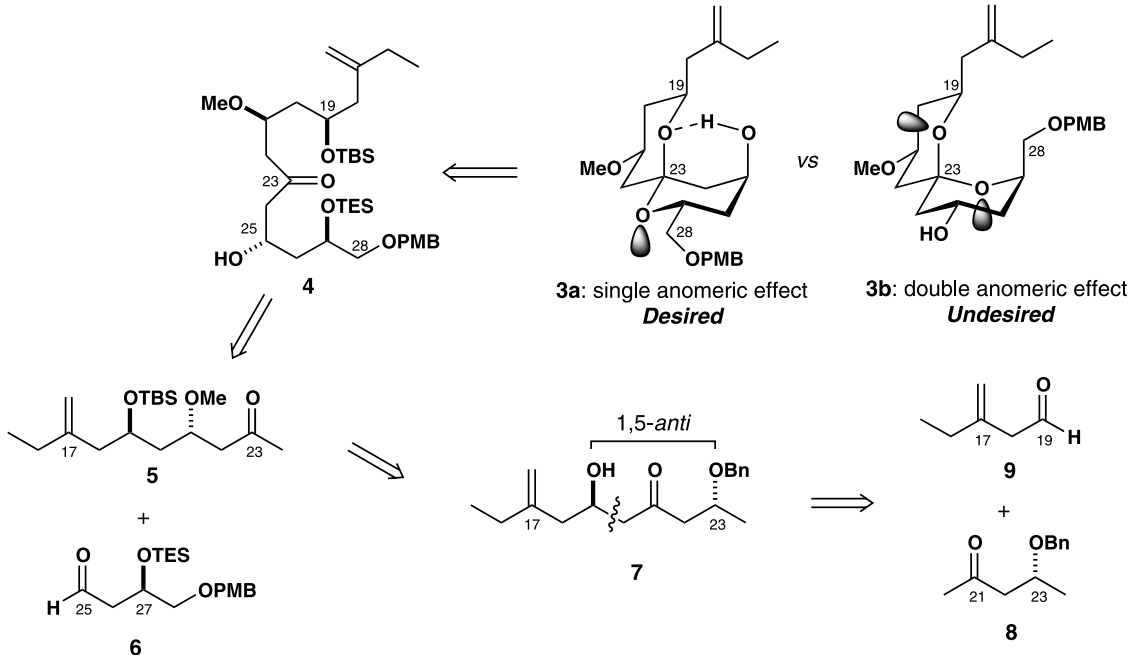
The synthesis began with the regioselective enolisation of methyl ketone **8**,[9] using (+)-Ipc_2BCl and Et_3N,[10] to give enol borinate **10** in situ (Scheme 3).[11] Reaction of **10** with aldehyde **9**,[12] followed by oxidative workup, provided the 1,5-*anti* aldol adduct **7** as the predominant diastereomer (91:9 dr), in 51% yield (unoptimised).[13] The stereogenicity at C_{19} and degree of diastereoselectivity were determined by ^1H NMR analysis of the (*R*)- and (*S*)-MTPA esters,[14] and conform to the levels of 1,5-*anti* selectivity generally observed for aldol reactions of this type.[8] Gratifyingly, no isomerisation of aldehyde **9** to the α,β-unsaturated isomer was observed under the reaction conditions, illustrating the mild nature of the boron mediated aldol reaction.[15]

The Evans–Tishchenko reduction[16] was chosen as the most appropriate method for conversion of β-hydroxyketone **7** to the mono-protected 1,3-*anti* diol **11**. Preliminary experiments utilising benzaldehyde as the hydride source were slow and low yielding. However, the use of propionaldehyde and catalytic SmI_2 proved efficient, allowing for the production of **11** in good yield (90%) and with an excellent level of 1,3-stereoinduction (>97:3 dr).

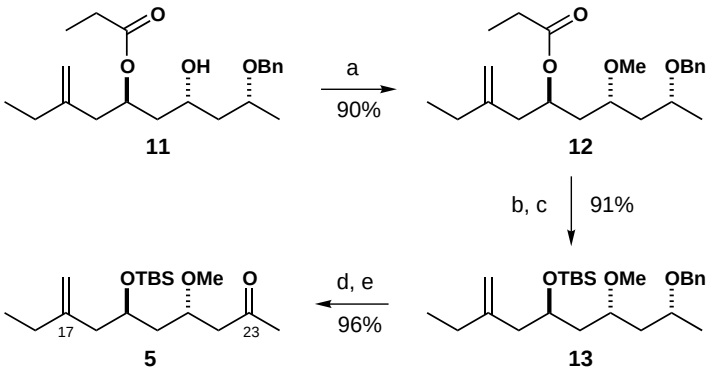
Methylation of alcohol **11** required the use of very mild, near neutral conditions (Scheme 4).[17] Subjection of **11** to MeOTf and 2,6-di-*tert*-butylpyridine in refluxing CH_2Cl_2 proved successful, although the yield was moderate (65%), reaction times were prolonged (16 h) and unwanted byproducts were apparent. Much more satisfactory was the use of trimethyloxonium tetrafluoroborate and Proton-Sponge® in CH_2Cl_2, affording methyl ether **12** rapidly (3 h, 0°C) and in good yield (90%).



Scheme 3. (a) (+)-Ipc_2BCl, Et_3N, Et_2O, −78→0°C, 1 h; (b) **9**, Et_2O, −78→−20°C, 90 min; H_2O_2, MeOH, pH 7 buffer, 20°C, 1 h; (c) SmI_2 (cat.), EtCHO, THF, −20°C, 16 h.



Scheme 2. Retrosynthetic analysis.



Scheme 4. (a) Me_3OBF_4, Proton-Sponge®, CH_2Cl_2, 0°C, 3 h; (b) K_2CO_3, MeOH, 20°C, 16 h; (c) TBSCl, Im, DMF, 20°C, 16 h; (d) LiDBB, THF, −78°C, 1 h; (e) Dess–Martin periodinane, pyr., CH_2Cl_2, 20°C, 40 min.

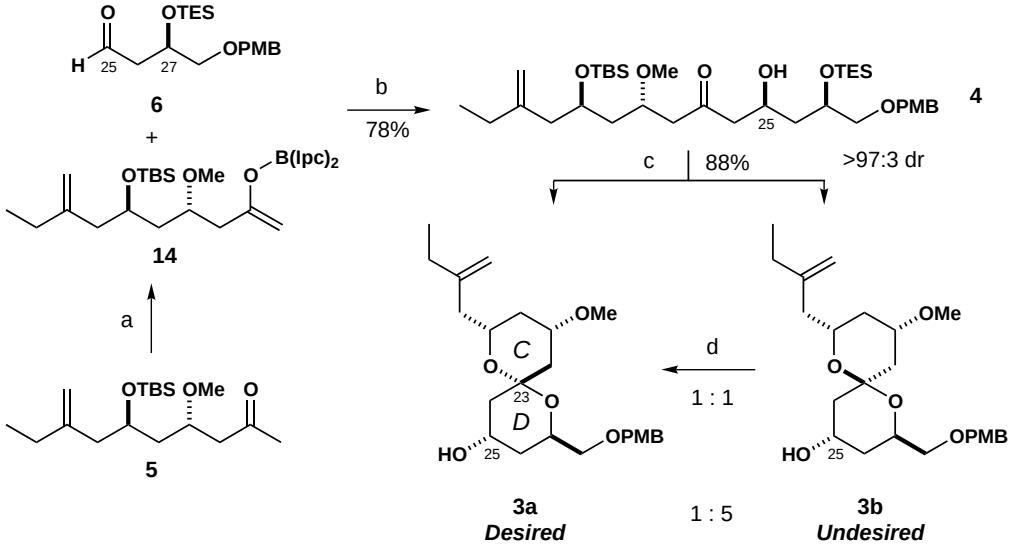
Exchange of the propionate in **12** for a TBS protecting group proceeded smoothly, providing **13** (91%). Subsequent removal of the benzyl ether utilising LiDBB[18] and oxidation of the resultant alcohol with Dess–Martin periodinane[19] produced ketone **5** (96%), ready for aldol coupling.

The boron-mediated aldol reaction of aldehyde **6** with ketone **5** was well precedented from our previously published route to the CD-spiroacetal subunit **2**.[6c] In the event, treatment of ketone **5** with (−)-Ipc_2BCl and Et_3N led to regioselective enolisation to give enol borinate **14** in situ (Scheme 5). Reaction of this with aldehyde **6**, followed by oxidative workup, gave the linear C_{16}–C_{28} fragment **4**[13] (78% yield) as the only identifiable diastereomer (>97:3 dr). Notably, this boron-mediated aldol reaction exploits triple asymmetric induction, where the influence of all three chiral components (aldehyde, ketone and boron reagent) are matched.

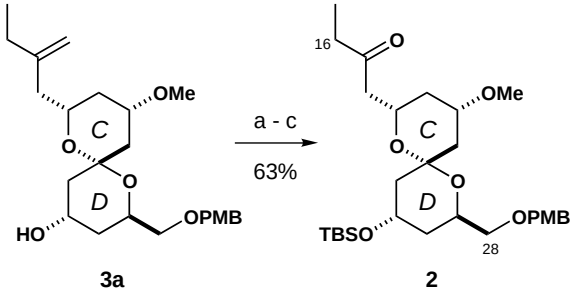
Treatment of **4** with aqueous HF in acetonitrile led to the smooth formation of spiroacetals **3a** and **3b** (1:5, 88% yield). Under anhydrous acid conditions (HCl, CH_2Cl_2) the spiroacetals equilibrated to a ca. 1:1 mixture, and were readily separable by flash chromatography (43% of the desired isomer **3a** and 33% of **3b**). The undesired isomer **3b** could then be re-equilibrated to give more of **3a**.

With CD-spiroacetal **3a** in hand, bearing the correct stereochemistry at the anomeric centre (C_{23}), conversion to the required subunit **2** was straightforward. Protection of **3a** as the corresponding TBS ether was achieved with TBSOTf and 2,6-lutidine (Scheme 6). Dihydroxylation with catalytic OsO_4 and NMO as co-oxidant, followed by sodium periodate cleavage of the resultant diol, provided the desired CD-spiroacetal subunit **2** (63%, three steps), identical in all respects with material provided by our earlier route.[6c]

In conclusion, the CD-spiroacetal containing C_{16}–C_{28} subunit **2** was prepared in this new route in 11.8% yield over 13 steps from ketone **8**. The synthesis presented here further illustrates the utility of the boron-mediated aldol reaction for the stereoselective construction of



Scheme 5. (a) (−)-Ipc_2BCl, Et_3N, Et_2O, −78→0°C, 1 h; (b) **6**, Et_2O, −78→−20°C, 16 h; H_2O_2, MeOH, pH 7 buffer, 20°C, 1 h; (c) $HF_{(aq)}$, MeCN, 0°C, 40 min; (d) HCl (cat.), CH_2Cl_2, 20°C, 30 min.



3a 2

Scheme 6. (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 1 h; (b) OsO_4 (cat.), NMO, Me_2CO/H_2O, 20°C, 6 h; (c) $NaIO_4$, MeOH/pH 7 buffer, 20°C, 1 h.

polyacetate subunits.[20] Combined with the highly stereoselective and hydroxyl discriminating Evans–Tishchenko reduction, this provides a powerful tool for the synthesis of polyketide natural products. Additionally, the use of sensitive β,γ-unsaturated aldehydes in the boron-mediated aldol reaction has been shown to be effective.

Acknowledgements

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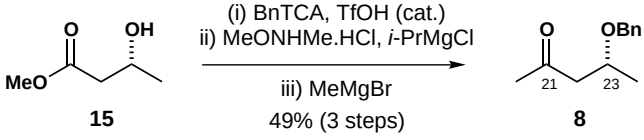
References

1. For key references on the isolation, structure elucidation and biological activity of the altohyrtins, spongistatins and cinachyrolide A, see: (a) Kobayashi, M.; Aoki, S.; Sakai, K.; Kawazoe, K.; Kihara, N.; Sasaki, T.; Kitagawa, I. *Tetrahedron Lett*. **1993**, *34*, 2795–2798; (b) Kobayashi, M.; Aoki, S.; Gato, K.; Kitagawa, I. *Chem. Pharm. Bull*. **1996**, *44*, 2142–2149; (c) Pettit, G. R.; Chicacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. *J. Org. Chem*. **1993**, *58*, 1302–1304; (d) Bai, R.; Cichacz, Z. A.; Herald, C. L.; Pettit, G. R.; Hamel, E. *Mol. Pharmacol*. **1993**, *44*, 757–766; (e) Bai, R.; Taylor, G. F.; Cichacz, Z. A.; Herald, C. L.; Kepler, J. A.; Pettit, G. R.; Hamel, E. *Biochemistry* **1995**, *34*, 9714–9721; (f) Fusetani, N.; Shinoda, K.; Matsunaga, S. *J. Am. Chem. Soc*. **1993**, *115*, 3977–3981.
2. For reviews see: (a) Pietruszka, J. *Angew. Chem., Int. Ed*. **1998**, *37*, 2629–2636; (b) Norcross, R. D.; Paterson, I. *Chem. Rev*. **1995**, *95*, 2041–2114.
3. (a) Evans, D. A.; Coleman, P. J.; Dias, L. C. *Angew. Chem., Int. Ed*. **1997**, *36*, 2738–2741; (b) Evans, D. A.; Trotter, B. W.; Cote, B.; Coleman, P. J. *Angew. Chem., Int. Ed*. **1997**, *36*, 2741–2744; (c) Evans, D. A.; Trotter, B. W.; Cote, B.; Coleman, P. J.; Dias, L. C.; Tyler, A. N. *Angew. Chem., Int. Ed*. **1997**, *36*, 2744–2747; (d) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Cote, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671–8726.
4. (a) Smith, A. B., III; Doughty, V. A.; Lin, Q.; Zhuang, L.; McBriar, M. D.; Boldi, A. M.; Moser, W. H.; Murase, N.; Nakayama, K.; Sobukawa, M. *Angew. Chem., Int. Ed*. **2001**, *40*, 191–195; (b) Smith, A. B., III; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Kerns, J. K.; Brook, C. S.; Murase, N.; Nakayama, K. *Angew. Chem., Int. Ed*. **2001**, *40*, 196–199.
5. (a) Guo, J.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi, Y. *Angew. Chem., Int. Ed*. **1998**, *37*, 187–192; (b) Hayward, M. M.; Roth, R. M.; Duffy, K. J.; Dalko, P. I.; Stevens, K. L.; Guo, J.; Kishi, Y. *Angew. Chem., Int. Ed*. **1998**, *37*, 192–196.
6. (a) Paterson, I.; Chen, D. Y.-K.; Coster, M. J.; Aceña, J. L.; Bach, J.; Gibson, K. R.; Keown, L. E.; Oballa, R. M.; Trieselmann, T.; Wallace, D. J.; Hodgson, A. P.; Norcross, R. D. *Angew. Chem., Int. Ed*. **2001**, *40*, 4055–4060; (b) Paterson, I.; Wallace, D. J.; Oballa, R. M. *Tetrahedron Lett*. **1998**, *39*, 8545–8548; (c) Paterson, I.; Wallace, D. J.; Gibson, K. R. *Tetrahedron Lett*. **1997**, *38*, 8911–8914; (d) Paterson, I.; Oballa, R. M. *Tetrahedron Lett*. **1997**, *38*, 8241–8244; (e) Paterson, I.; Keown, L. E. *Tetrahedron Lett*. **1997**, *38*, 5727–5730; (f) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett*. **1996**, *37*, 8581–8584.
7. Syntheses of the CD-spiroacetal subunit by other groups: (a) Hayes, C. J.; Heathcock, C. H. *J. Org. Chem*. **1997**, *62*, 2678–2679; (b) Paquette, L. A.; Braun, A. *Tetrahedron Lett*. **1997**, *38*, 5119–5122; (c) Crimmins, M. T.; Katz, J. D. *Org. Lett*. **2000**, *2*, 957–960; (d) Zemribo, R.; Mead, K. T. *Tetrahedron Lett*. **1998**, *39*, 3895–3898; (e) Terauchi, T.; Terauchi, T.; Sato, I.; Tsukada, T.; Kanoh, N.; Nakata, M. *Tetrahedron Lett*. **2000**, *41*, 2649–2653.
8. (a) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett*. **1996**, *37*, 8585–8588; (b) Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem*. **1997**, *62*, 788–789.
9. Ketone **8** was prepared in enantiomerically pure form in three steps from methyl (*R*)-3-hydroxybutyrate (**15**):



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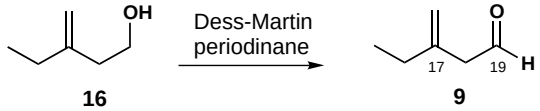
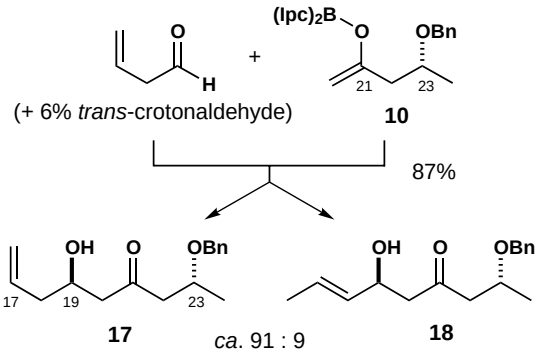
10. Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663–4684.
11. For reviews on asymmetric aldol reactions using boron enolates, see: (a) Cowden, C. J.; Paterson, I. *Org. React*. **1997**, *51*, 1–200; (b) Paterson, I.; Cowden C. J.; Wallace, D. J. In *Modern Carbonyl Chemistry*; Otera, J., Ed; Wiley-VCH: Weinheim, 2000; pp. 249–297.
12. Aldehyde **9** was synthesised by Dess–Martin oxidation of the known alcohol **16**: Alexakis, A.; Normant, J.; Villieras, J. *J. Organomet. Chem*. **1975**, *96*, 471–485.



16 9

13. All new compounds gave spectroscopic data in agreement with the assigned structures. **4** had: $[\alpha]_D^{20}$ −2.5 (*c* 1.69, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (2H, d, $J=8.6$ Hz), 6.87 (2H, d, $J=8.6$ Hz), 4.77 (1H, d, $J=1.4$ Hz), 4.72 (1H, br s), 4.44 (2H, s), 4.23 (1H, m), 4.07 (1H, m), 3.97 (1H, m), 3.87 (1H, m), 3.80 (3H, s), 3.52 (1H, d, $J=2.2$ Hz), 3.41 (1H, dd, $J=9.7$, 5.1 Hz), 3.37 (1H, dd, $J=9.7$, 5.1 Hz), 3.28 (3H, s), 2.72 (1H, dd, $J=15.8$, 6.5 Hz), 2.60 (1H, dd, $J=16.7$, 7.9 Hz), 2.53 (1H, dd, $J=16.7$, 4.3 Hz), 2.48 (1H, dd, $J=15.8$, 5.5 Hz), 2.30 (1H, dd, $J=13.6$, 4.7 Hz), 2.10 (1H, dd, $J=13.6$, 4.7 Hz), 1.99 (2H, br q, $J=7.3$ Hz), 1.61–1.73 (3H, m), 1.34 (1H, ddd, $J=14.2$, 8.8, 3.8 Hz), 1.02 (3H, t, $J=7.4$ Hz), 0.93 (9H, t, $J=8.0$ Hz), 0.90 (9H, s), 0.60 (6H, q, $J=8.0$ Hz), 0.08 (3H, s), 0.07 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 209.1, 159.2, 147.9, 130.1, 129.3, 113.7, 110.8, 74.2, 73.9, 73.0, 70.6, 67.9, 66.0, 56.4, 55.2, 50.8, 48.5, 45.4, 42.0, 41.1, 29.0, 25.9, 18.0, 12.2, 6.8, 4.9, −4.1, −4.6; HRMS (+ESI) Calcd for $C_{36}H_{66}O_7Si_2Na$ $[M+Na]^+$: 689.4245, found: 689.4234.
14. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
15. In a preliminary experiment, reaction of enol borinate **10** with 3-butenal (94:6 mixture with *trans*-crotonaldehyde) gave aldol adduct **17** as a mixture (ca. 91:9) with **18** (resulting from reaction with *trans*-crotonaldehyde):



16. Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449.
17. Mild conditions for the methylation of alcohols: Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *Tetrahedron Lett.* **1994**, *35*, 7171–7172.
18. Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854–860.
19. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
20. For related work, see: Paterson, I.; Collett, L. A. *Tetrahedron Lett.* **2001**, *42*, 1187–1191.