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Application of hitherto unexplored macrocyclization strategies in the epothilone series: novel epothilone analogs by total synthesis†

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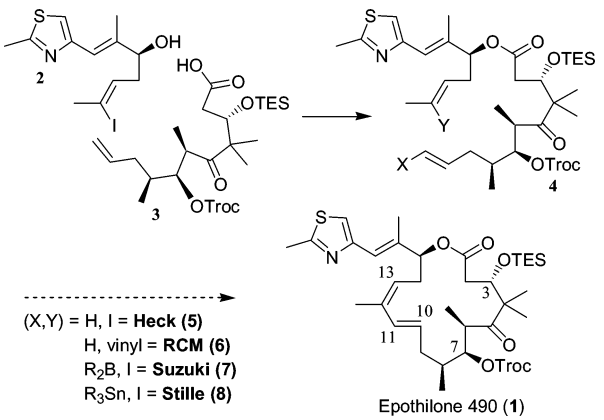
A total synthesis of Epothilone 490 and a synthesis of 11-hydroxy dEpoB utilizing a vinyl-boronate cross-metathesis followed by a Suzuki macrocyclization. A mild route to reach aldehydes from terminal olefins, anticipating Nozaki–Kishi macrocyclization is described.

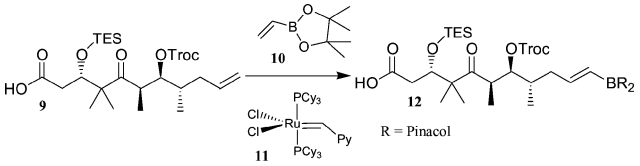
Recently we described our total synthesis of the novel Epothilone 490 (**1**) employing diene–ene ring closing metathesis (RCM) reaction. We also reported a rudimentary SAR profile of the otherwise underexplored C10–C11 region of the epothilones.[1] Simultaneously we exploited other synthetic macrocyclization approaches toward Epothilone 490 (Scheme 1). In addition to the RCM method, we also considered Heck-, Stille- and Suzuki-macrocyclizations. None of these had previously been reported in the burgeoning epothilone literature.[1,2] From our established synthetic intermediates (**2** and **3**),[2] the Heck marcrocyclization strategy (**5**) could provide access to Epo490 most rapidly, since it uses previously fashioned building blocks. The RCM method (**6**) on the other hand required transforming the vinyl iodide **2** into an ethylene unit as had been described. Application of Suzuki- (**7**) and Stille (**8**) macrocyclizations would require conversion of the terminal olefin in **3** to the corresponding vinyl-borane and vinyl-stannane, a non-trivial undertaking in this complex setting.



Scheme 1 Macrocyclization strategies for Epo490.

Simple acylation of our previously described *O*-alkyl (**2**) and *O*-acyl (**3**) fragments afforded the macro-Heck substrate (**5**). Unfortunately all attempts to effect the desired cyclization met with failure. We then turned our attentions to constructing the seco pre-Stille- and pre-Suzuki substrates. Toward achieving this goal, it was necessary to transform the terminal vinyl group into the corresponding *trans* stannane or borane. The most obvious way to accomplish this would pass through the corresponding alkyne, anticipating hydroboration[3a] or hydrostannylation.[3b,c] The alkyne needed could be readily reached *via* ozonolysis and homologation of an ester version of **3**. Alternatively, the same aldehyde could be used in a chromium initiated condensation with the corresponding boron[4a] and tin[4b] reagents.

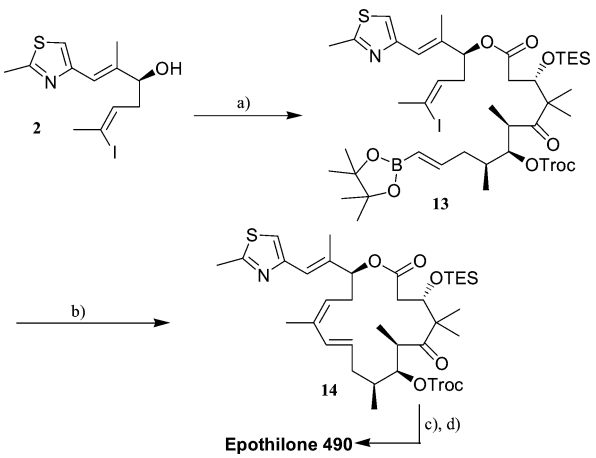
We wondered if such goals could be accomplished in an even simpler and general way. We took note of a report by Grubbs and coworkers in which was described a cross metathesis (CM) between a terminal olefin and a vinyl-pinacol boronate ester.[5a,b] Applied to our case, this method would provide the corresponding boronate in only one step from the terminal alkene.



Scheme 2 Cross metathesis with vinylboronate ester.

We tested the applicability of acid **9** to conditions reported by Grubbs and were delighted to find that use of the 'first' (**11**)[6a,b] and the 'second' generation[7a,b] Grubbs catalysts generated the desired vinylboronate ester **12** almost exclusively as the *trans* adduct. Since it was awkward to separate acid **9** from acid **12** it was important to drive the metatheses reaction to completion. We found that by recourse to catalyst **11** and by increasing the amount of boronate ester (**10**) used, this goal could be accomplished (93% isolated yield of **12**) (Scheme 2).[8]

With this encouraging CM-result in hand, efforts were then directed to evaluating the feasibility of using a Suzuki-macrocyclization to synthesize epothilone 490. These studies are detailed in Scheme 3. Allylic alcohol **2** was acylated with cross-metathesis product **12** to furnish the desired Suzuki substrate **13**. After screening a number of conditions, to effect the desired macrocyclization we found that Ag_2O–$Pd(PPh_3)_4$ could accomplish our goal albeit in only moderate yield (35%).[9,10] Deprotection, following our previously published protocols, provided epothilone 490.



Scheme 3 *Reagents and conditions*: (a) EDCI, DMAP, **2**, CH_2Cl_2, rt, 2 h, 67%; (b) $Pd(PPh_3)_4$, Ag_2O, THF, reflux, 5 h, 35%; (c) Zn))), THF–AcOH (1 : 1), rt, 30 min, 95%; (d) HF·pyridine, THF, rt, 5 h, 90%.

† Electronic supplementary information (ESI) available: experimental details for the synthesis of **14** and **32**. See http://www.rsc.org/suppdata/cc/b2/b209941a/

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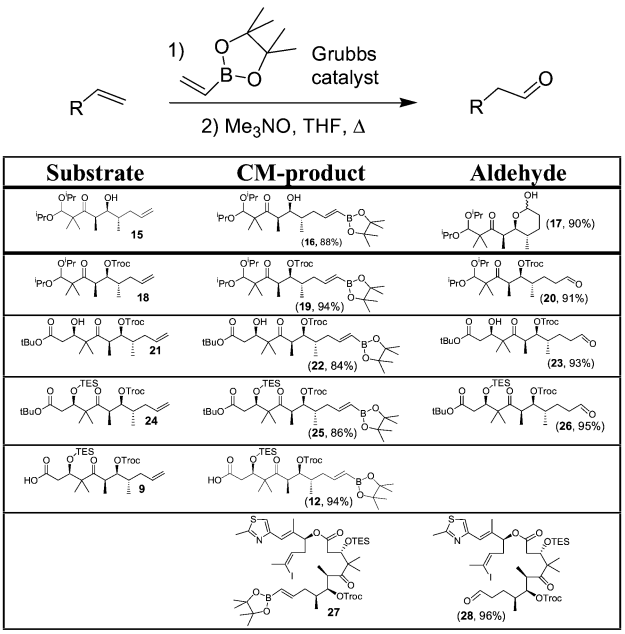
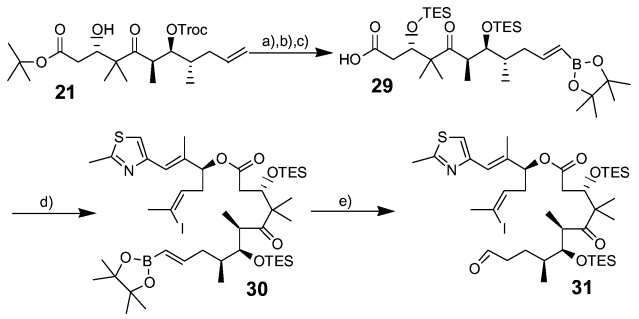
Previously, we had been able to chemoselectively hydrogenate, dihydroxylate and cyclopropanate the newly generated[10,11] double bond in Epo490. However, all efforts at selective hydration across the olefin linkage met with no success. We were especially interested in the 11-hydroxy dEpoB (11-OH) since it had come to our attention[11] that one of the two possible 11-OH dEpoB diastereomers was as active as our current Phase I clinical candidate dEpoB. Parallel with our attempted hydration studies, we had attempted incorporation of a pre 11-hydroxy group using RCM.[12] Unfortunately, the required substrate did not undergo the projected RCM. We sought a new synthetic route to achieve the functionalization pattern.

We were particularly intrigued by the possibility of accomplishing this goal *via* a Nozaki–Kishi[13] macrocyclization. This reaction has been shown to be compatible with complex functional group arrays. In order to evaluate this means of cyclization, we had to find a mild way to convert our vinylboronate ester (**13**) to the corresponding aldehyde. In combination with CM this sequence would present an alternative to the widely practised hydroboration–oxidation method for converting terminal olefins to aldehydes. There are a number of oxidants that have been used to convert vinylboranes to their corresponding carbonyl functionalities. We required a transformation that would be compatible with our heavily functionalized Suzuki substrate. In screening known oxidants, we found that trimethylamine *N*-oxide[14] was the most attractive for several reasons. First it seemed to tolerate all the functional groups that we tested, furthermore it could be used in excess if needed and finally the work up was very simple. Shown in Table 1 are several examples that underscore how well this method works. These few examples demonstrate compatibility with hydroxyls (**15** and **21**), acids (**9**) and ketone functional groups. Most importantly, the method allows for oxidizing a terminal olefin to an aldehyde without protection of a resident alcohol. This condition, superimposed on an already complex setting would be a challenging problem, in the context of the traditional hydroboration–oxidation sequence.

Table 1 Cross metathesis–oxidation‡



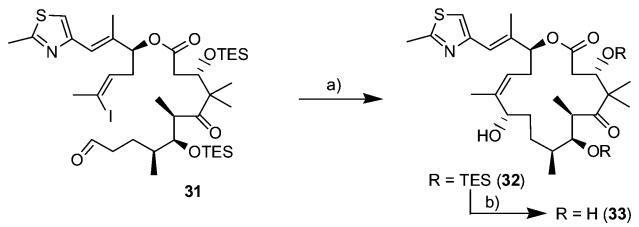
Unfortunately our newly formed Nozaki–Kishi substrate **28** did not produce any of the desired cyclization product. We attributed these problems to the Troc-protecting group, *i.e.* the trichloro unit not being compatible with the reaction conditions. Following this interpretation of this problem, we chose to introduce a more compatible C-7 protecting group at an earlier stage. Shown in Scheme 4 is the synthesis of compound **31**, our new candidate for chromium–nickel mediated macrocyclization.



Scheme 4 *Reagents and conditions*: (a) Zn))), THF–AcOH (1:1), rt, 30 min, 93%; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, rt, 2 h, 65%; (c) **10**, **11** (cat.), CH_2Cl_2, reflux, 10 h, 85%; (d) EDCI, DMAP, **2**, CH_2Cl_2, rt, 1 h, 65%; (e) Me_3NO, THF, reflux, 4 h, 95%.

The Troc group in compound **21** was removed. Both alcohols were protected as TES-ethers and the ester was deprotected. The terminal alkene was converted to the vinyl-boronate ester **29** as previously described. The resulting acid was coupled to iodo-alcohol **2** to furnish **30**. The latter was then subjected to the Me_3NO oxidation conditions, as described above, to afford Nozaki–Kishi macrocyclization substrate **31**.

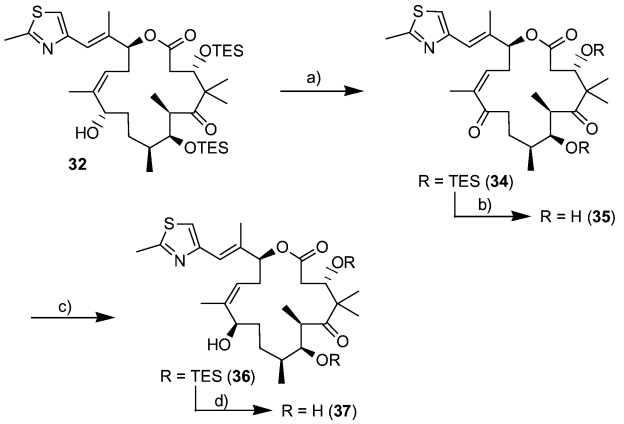
Previously our lab had employed a Nozaki–Kishi macrocyclization reaction for construction of the nine membered ring moiety in our total synthesis of eleutherobin.[15] These conditions were not successful in the case at hand where we sought to generate a much larger ring. There are notably few examples of Nozaki–Kishi macrocyclizations beyond 12 membered rings in the literature.[16] After extensive experimentation, we used conditions similar to those used by Uguen[16e] in his total synthesis of the 16-membered macrolide spiramycin. As shown (Scheme 5), the macrocyclization proceeded smoothly and *produced only one isolated 11-OH diastereomer* (**32**). This diastereomer was derivatized as its (*R*)- and (*S*)-MPA ester and analyzed according to formats of Trost[17a] and Riguera.[17b,c] This analysis allowed for assignment of the (*S*) configuration of the newly formed C_{11} stereocenter. Global deprotection of **32** produced triol **33**.



Scheme 5 *Reagents and conditions*: (a) $CrCl_2$, $NiCl_2$, DMF–THF (3:1), rt, 5 h, 40%; (b) HF·pyridine, THF, rt, 5 h, 85%.

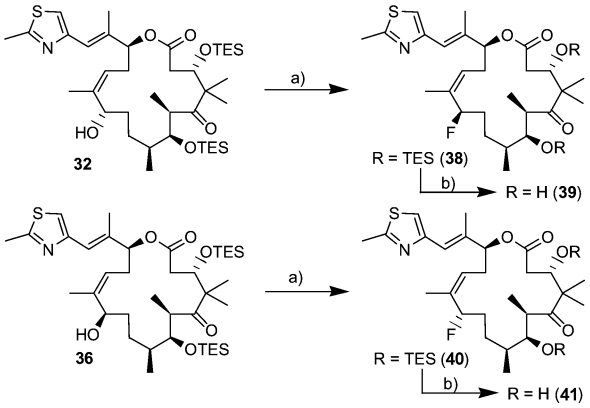
Our goal had been to access both α and β 11-hydroxyl dEpoB and to evaluate their potency. Since the Nozaki–Kishi macrocyclization was stereoselective, we required an alternative route to reach the C_{11} (*R*) diastereomer. We wondered whether 1,2-reductions of the hypothetical C_{11} ketone could be achieved and whether it would provide access to the desired (*R*) diastereomer. Towards this end, alcohol **32** was oxidized cleanly to enone **34** (Scheme 6). Upon retrospective evaluation with the aid of computational techniques, we concluded that **36** could find energy minima in conformations in which the macrocyclic framework blocks the approach of the incoming nucleophile from the α-face of the system, resulting in clean formation of **36**. Compound **36** was converted, following cleavage of the C_3 and C_7 silyl groups, to (*R*)-11-hydroxy dEpoB (**33**). The latter was identical in all respects to an authentic sample provided by Kosan Biosciences.[18]

Having gained access to both 11-hydroxy dEpoB diasteromers, as well as to the corresponding enone, we took advantage of these flexible handles for further functionalization. We



Scheme 6 *Reagents and conditions*: (a) Dess–Martin periodinane, CH_2Cl_2, rt, 6 h, 95%; (b) HF·pyridine, THF, rt, 5 h, 90%; (c) $NaBH_4$, $CeCl_3$, THF, −78 °C, 1 h, 75%; (d) HF·pyridine, THF, rt, 4 h, 85%.

undertook to convert the 11-alcohol groups to 11-fluoro functions and to compare the activity of the corresponding 11-hydroxy and 11-fluoro functions. Towards that end, both 11-hydroxy diastereomers were subjected to treatment with DAST (Scheme 7), thus affording the corresponding 11-fluoro analogs.[19] Global deprotection was achieved smoothly, yielding the desired 11-fluoro dEpoB diastereomers (**39** and **41** respectively) in high yield.



Scheme 7 *Reagents and conditions*: (a) DAST, CH_2Cl_2, −78 °C, 30 min (**38** 55%, **40** 65%); (b) HF·pyridine, THF, rt, 4 h (**39** 86%, **41** 90%).

The *in vitro* and *in vivo* activity of these new analogs along with their pharmacological properties is quite interesting and will be reported in due course.

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Notes and references

‡ Typical procedure for synthesis of aldehydes using CM–oxidation sequence: to a stirred solution of **18** (167 mg, 0.33 mmol, 1 equiv.) in CH_2Cl_2 (3.5 mL) was added **10** (152 mg, 0.99 mmol, 3 equiv.) and **11** (27 mg, 0.033 mmol, 0.1 equiv.). This mixture was refluxed for 8 h at which point it was cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and stripped onto silica gel. Purification on silica employing an EtOAc–hexanes gradient afforded pure **19** (195 mg, 94%): IR (neat) 2976, 2933, 1760, 1696, 1637, 1461, 1381, 1325, 1243, 1143, 1037, 928 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.50 (m, 1H), 5.43 (d, J = 17.9 Hz, 1H), 4.93 (t, J = 5.9 Hz, 1H), 4.83 (d, J = 12.0 Hz, 1H), 4.73 (d, J = 12.0 Hz, 1H), 4.56 (s, 1H), 3.83–3.78 (m, 2H), 3.53–3.47 (m, 1H), 2.42–2.38 (m, 1H), 1.97–1.90 (m, 1H), 1.87–1.82 (m, 1H), 1.24–1.22 (m, 15H), 1.19 (d, J = 6.1 Hz, 3H), 1.15 (d, J = 6.1 Hz, 3H), 1.14 (d, J = 6.1 Hz, 3H), 1.06 (m, 9H), 0.93 (d, J = 6.7 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 215.9, 154.7, 152.2, 103.8, 95.2, 83.8, 83.7, 83.5, 77.0, 71.3, 70.0, 54.4, 42.8, 38.3, 34.8, 25.2, 25.1, 23.9, 23.7, 22.7, 22.2, 21.9, 19.8, 16.9, 12.7; HRMS (FAB) calcd. For $C_{28}H_{48}BCl_3NaO_8$ (M + Na^+) 651.2405, found 651.2386.

To a stirred solution of **19** (40 mg, 0.064 mmol, 1 equiv.) in THF (1.0 mL) was added trimethyl *N*-oxide (24 mg, 0.317 mmol, 5 equiv.). This mixture was refluxed for 4 h at which point it was cooled to room temperature. Water (2.0 mL) was added and stirring was continued for another 1 h, before adding CH_2Cl_2 (10 mL) and separating the layers. The aqueous layer was extracted twice with CH_2Cl_2 (10 mL) and the combined organic layers were dried over Na_2SO_4 to afford aldehyde **20** (30 mg, 91%): IR (neat) 2978, 2932, 1759, 1725, 1685, 1460, 1378, 1249, 1126, 1038, 926, 816 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 4.94 (t, J = 6.0 Hz, 1H), 4.86 (d, J = 12.0 Hz, 1H), 4.71 (d, J = 12.0 Hz, 1H), 4.55 (s, 1H), 3.82–3.80 (m, 2H), 3.54–3.50 (m, 1H), 2.57–2.50 (m, 1H), 2.41–2.34 (m, 1H), 1.88–1.77 (m, 2H), 1.54–1.46 (m, 1H), 1.23 (s, 3H), 1.19 (d, J = 6.1 Hz, 3H), 1.16 (d, J = 6.1 Hz, 3H), 1.14 (d, J = 6.1 Hz, 3H), 1.10 (s, 3H), 1.08 (d, J = 6.9 Hz, 3H), 1.07 (d, J = 6.1 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 215.5, 202.0, 154.2, 103.4, 94.7, 83.0, 76.6, 70.8, 70.0, 53.9, 42.3, 41.2, 34.2, 23.4, 23.3, 22.2, 21.6, 19.7, 16.2, 12.2; HRMS (FAB) calcd. For $C_{22}H_{37}Cl_3NaO_7$ (M + Na^+) 541.1503, found 541.1518.

1 K. Biswas, H. Lin, J. T. Njardarson, M. D. Chappell, T.-C. Chou, Y. Guan, W. P. Tong, L. He, S. B. Horwitz and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2002, **124**, 9825 and references cited therein.
2 C. B. Lee, Z. Wu, F. Zhang, M. D. Chappell, S. Stachel, T.-C. Chou, Y. Guan and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2001, **123**, 5249 and references cited therein.
3 (*a*) H. C. Brown, *Organic Synthesis via Boranes*, John Wiley & Sons, New York, 1975; (*b*) H. X. Zhang, F. Guibe and G. Balavoine, *J. Org. Chem.*, 1990, **55**, 1857; (*c*) C. D. J. Boden, G. Pattenden and T. Ye, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2417.
4 (*a*) K. Takai, N. Shinomiya, H. Kaihara, N. Yoshida and T. Moriwake, *Synlett*, 1995, 963; (*b*) D. M. Hodgson, L. T. Boulton and G. N. Maw, *Tetrahedron Lett.*, 1994, **35**, 2231.
5 (*a*) H. E. Blackwell, D. J. O'Leary, A. K. Chatterjee, R. A. Washenfelder, D. A. Bussmann and R. H. Grubbs, *J. Am. Chem. Soc.*, 2000, **122**, 58; (*b*) A. K. Chatterjee and R. H. Grubbs, *Angew. Chem., Int. Ed.*, 2002, **41**, 3172.
6 (*a*) P. Schwab, M. B. France, J. W. Ziller and R. H. Grubbs, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2039; (*b*) R. H. Grubbs, S. J. Miller and G. C. Fu, *Acc. Chem. Res.*, 1995, **28**, 446.
7 (*a*) M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953; (*b*) A. K. Chatterjee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 1751.
8 We also tried to reach the seco-Stille substrate *via* cross metathesis by reacting the same terminal olefin with vinyltributyltin, but those efforts were not successful.
9 For the effect of silver oxide on palladium-catalyzed cross couplings see: T. Gillmann and T. Weeber, *Synlett*, 1994, 649.
10 For similar sp^2–sp^2 Suzuki macrocyclizations see: (*a*) J. D. White, R. Hanselmann, R. W. Jackson, W. J. Porter, Y. Ohba, T. Tiller and S. Wang, *J. Org. Chem.*, 2001, **66**, 5217; (*b*) A.-C. Carbonnelle and J. Zhu, *Org. Lett.*, 2000, **2**, 3477; (*c*) V. Lobregat, G. Alcaraz, H. Bienayme and M. Vaultier, *Chem. Commun.*, 2001, 817.
11 Kosan Bioscience.
12 This was done by simply performing a Stille reaction using ethoxyvinyltin instead of vinyltin as described in ref. 1. In an attempted ring closing metathesis reaction, only cross metathesis and dimerization of the terminal olefin was observed.
13 (*a*) H. Jin, J.-I. Uenishi, W. J. Christ and Y. Kishi, *J. Am. Chem. Soc.*, 1986, **108**, 5644; (*b*) K. Takai, M. Tagashira, T. Kuroda, K. Oshima, K. Utimoto and H. Nozaki, *J. Am. Chem. Soc.*, 1986, **108**, 6048; (*c*) A. Furstner, *Chem. Rev.*, 1999, **99**, 991.
14 For the use of Me_3NO in organic synthesis see: *Encyclopedia of Reagents for Organic Synthesis*, ed. Leo A. Paquette, John Wiley & Sons, New York, 1995, vol. 7, p. 5197.
15 X.-T. Chen, S. K. Bhattacharya, B. Zhou, C. E. Gutteridge, T. R. R. Pettus and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1999, **121**, 6563.
16 (*a*) R. A. Pilli, C. K. Z. de Andrade, C. R. O. Souto and A. de Meijere, *J. Org. Chem.*, 1998, **63**, 7811; (*b*) K. M. Foote, J. Matthew and J. Pattenden, *Synlett*, 2001, 365; (*c*) W. D. P. Goldring and G. Pattenden, *Chem. Commun.*, 2002, 1736; (*d*) B. Mi and R. E. Maleczka, *Org. Lett.*, 2001, **3**, 1491; (*e*) G. Oddon and D. Uguen, *Tetrahedron Lett.*, 1998, **39**, 1157.
17 (*a*) B. M. Trost, R. C. Bunt and S. R. Pulley, *J. Org. Chem.*, 1994, **59**, 4202; (*b*) J. M. Seco, S. K. Latypov, E. Quinoa and R. Riguera, *Tetrahedron*, 1997, **53**, 8541; (*c*) J. M. Seco, E. Quinoa and R. Riguera, *Tetrahedron: Asymmetry*, 2000, **11**, 2781.
18 We thank Kosan Bioscience for providing sample of 11-OH dEpoB.
19 The selectivity for S_N2 *vs.* S_N2' was about 4:1 in both cases.