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Review

Computer-Assisted Design and Synthetic Applications of Chiral Enol Borinates: Novel, Highly Enantioselective Aldol Reagents

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Descrevemos recentemente o desenvolvimento de um modelo quantitativo de estados de transição para a previsão da estereosseletividade em condensações aldólicas mediadas por boro. Este modelo fornece percepções qualitativas sobre os fatores, contribuindo para o resultado estereoquímico de uma variedade de reações de importância sintética. O modelo de campo de força foi utilizado para auxiliar na elaboração e preparação de novos ligantes de boro quirais derivados da mentona. Os enolatos de boro quirais foram empregados em vários processos estereosseletivos, incluindo a adição a aldeídos quirais e a síntese total, controlada pelo reagente, da (3*S*,4*S*)-estatina. Os enolatos quirais derivados a partir de tioacetatos α-halo e α-oxisubstituídos foram adicionados a aldeídos e iminas. A adição de iminas leva à síntese enantiosseletiva de aziridinas quirais, a síntese total formal da (+)-tioamfenicol, a uma nova e altamente eficiente síntese da cadeia lateral em C-13 do paclitaxel (taxol®) e a semi-síntese do taxol a aprtir da bacatina III. O resultado estereoquímico da adição das iminas foi racionalizado com o auxílio de estudos computacionais. Reações de adição enantiosseletiva de enolatos de boro quirais derivados do tioacetato foram empregados com sucesso a aldeídos ligados à fase sólida, fornecendo produtos aldólicos em rendimentose enantiosseletividades comparáveis às condições usuais em solução.

We have recently described the development of a quantitative transition state model for the prediction of stereoselectivity in the boron-mediated aldol reaction. This model provides qualitative insights into the factors contributing to the stereochemical outcome of a variety of reactions of synthetic importance. The force field model was used to assist the design and preparation of new chiral boron ligands derived from menthone. The chiral boron enolates were employed in various stereoselective processes, including the addition to chiral aldehydes and the reagent-controlled total synthesis of (3*S*,4*S*)-statine. The chiral enolates derived from α-halo and α-oxysubstituted thioacetates were added to aldehydes and imines. Addition to imines leads to the enantioselective synthesis of chiral aziridines, a formal total synthesis of (+)-thiamphenicol, and a new highly efficient synthesis of the paclitaxel (taxol®) C-13 side-chain and taxol semisynthesis from baccatin III. The stereochemical outcome of the addition to imines was rationalised with the aid of computational studies. Enantioselective addition reactions of the chiral boron enolate derived from thioacetate have successfully been applied to solid phase bound aldehydes to give aldol products in comparable yields and enantioselectivities to the usual solution conditions.

Keywords: *chiral boron enolates, enantioselective aldol reactions, statine, paclitaxel*

Transition State Modeling and Design of New Boron Ligands

We recently described a force field model for the aldol reactions of ketone derived enol borinates with aldehydes. This force field is based on MM2, and on new parameters developed from *ab initio* calculations on the cyclic aldol transition structures (*e.g.* chair **1** and boats **2**, **3**; Fig. 1). The model reproduces the aldehyde *Si*: *Re* selectivity for the *syn* selective aldol reactions of a range of chiral *Z* enol borinates, as well as for the *anti* selective reactions of *E* enolates. The force field model suggested that the following factors were important in determining the stereoselectivity of the chiral boron-ligand mediated reactions: (a) the conformational rigidity of the boron-ligand, (b) the relative orientation of the ligands with respect to the transition structure core, and (c) the relative orientation and restrained rotation around the B-C bonds of one ligand relative to the other[1,2].

Based on this information, it was decided to search for conformationally locked systems. The case of *cis*-1,2-ethylisopropylcyclohexane appeared as an interesting example of conformational lock based on the avoidance of (+/-) double gauche pentane interactions (Fig. 2). There is only one conformation of the chair and of the side chains (**4**) that does not possess any (+/-) double gauche pentane interactions, while any other rotamer is higher in energy. The terminal methyl group of the ethyl side chain was substituted with a boron atom. For reasons of synthetic accessibility (see below), an extra equatorial methyl group was added to the ligand (**5**, Fig. 2), which did not alter the computed stereoselectivity.

After running the conformational search of a *Si:Re* face selection in an *E*(OB)-enol borinate reaction (for nomenclature see Ref. 3) leading to an *anti* aldol, we were delighted to discover that the new chiral enolates showed a distinct stereoselectivity in the computational run, surpassing by far Ipc (isopinocampheyl) or any other designed reagent[4].

The Menthone Derived Boron Reagents

The synthesis of the new reagents **6** and **7** (Fig. 3) took considerable effort to develop due to the need for separation from diastereomeric dialkylboranes formed in the hydroboration step. The minor diastereomeric haloboranes were shown both computationally and experimentally to be low-stereoselective reagents for the aldol reaction. Eventually the borane was purified by crystallization in ethyl ether at low temperature. The reagent is quite stable and is currently prepared uneventfully and stored as a stock solution in methylene chloride in the freezer.

Syn aldols, in boron enolate chemistry, are easily obtained with good enantioselectivity from chiral *Z*(OB)-enolates because they have only access to a single transition structure, chair **1**. High selectivity for *anti* or unsubstituted aldols is comparably more difficult to achieve because unsubstituted enolates and (partly) *E*(OB)-enolates may adopt a variety of transition structures, namely chair **1**, boat **2**, and boat **3** (Fig. 1). This competition among transition structures of similar energy (usually many conformers for each transition structure core-conformation **1**, **2**, and **3**) makes the stereochemical control of the reaction much more difficult to obtain. The chiral *E* enol borinates derived from the reagents shown in Fig. 3 gave rise to ketone-derived *anti*-aldols, which had eluded earlier attempts at

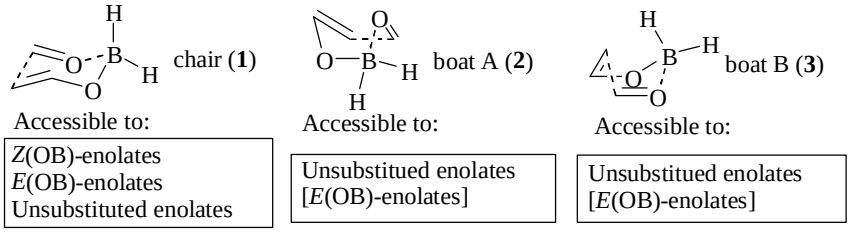


Figure 1. All-hydrogen substituted *ab initio* transition structures for boron enolate aldol addition.

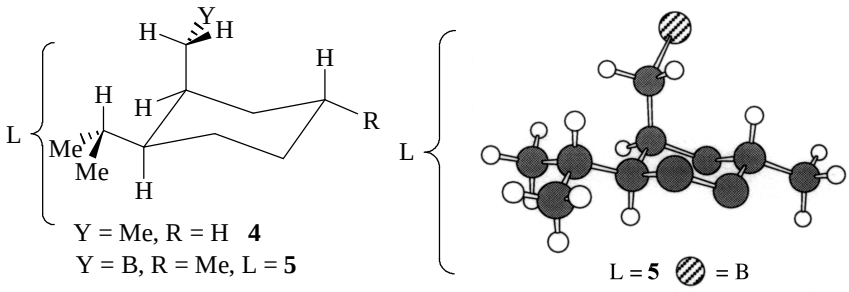


Figure 2. Lowest energy conformation of compound **4** and boron ligand **5**.

effective asymmetric synthesis via direct aldol-type condensation. Although the enantioselectivity was lower than computer-predicted (the aldol force field is not as calibrated with *E* enolates as it is with *Z* enolates), the enantiomeric excesses (74-88% e.e.; R = Me; R^1 = alkyl, aryl) were the highest reported for such transformations (Fig. 4). The reagent proved effective also with methyl ketone enolates leading to unsubstituted aldols, although with lower enantiomeric excesses (55-76% e.e.; R = H; R^1 = alkyl, aryl). Particularly noteworthy were the results with thioester-derived *anti* (≥ 98% e.e.; R = Me, R^1 = SBu^t) and unsubstituted aldols (87-97% e.e.; R = H, R^1 = SBu^t) (Fig. 4). The absolute configuration of the aldol products is consistent with chair transition structures, as suggested by the computer model (Fig. 4) [4-6].

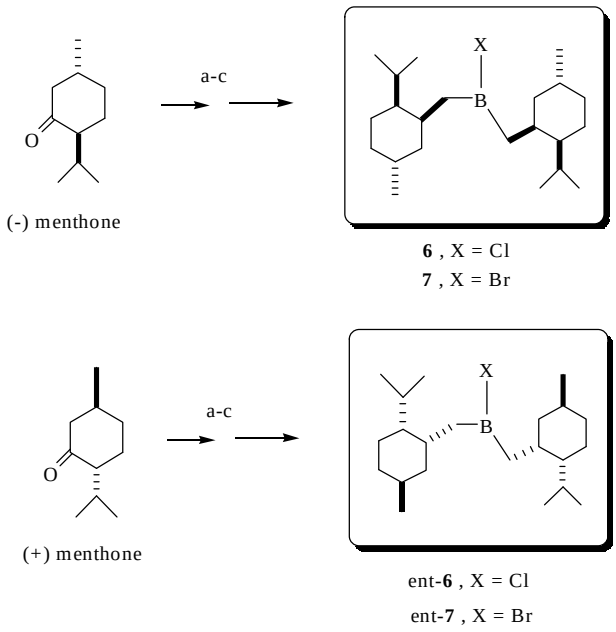


Figure 3. The menthone derived boron reagents. a) $Ph_3P=CH_2$; b) XBH_2-SMe_2, CH_2Cl_2; c) crystallization, Et_2O, -30 °C.

Reagent Control. Total Synthesis of (3*S*, 4*S*)-Statine

In the reaction of chiral enolates with chiral aldehydes the intrinsic diastereofacial selectivities of the two chiral components are either matched or mismatched. If the aldehyde (substrate) intrinsic selectivity is moderate and the enolate (reagent) selectivity is very high, reagent control is obtained. Boron enolates derived from **7** or ent-**7** show a high degree of reagent control in reactions with chiral aldehydes, and the efficiency of double asymmetric synthesis reflects the level of enantiomeric excess of the reactions with achiral aldehydes [thiopropionates (≥ 98% e.e.) ≥ thioacetates (87-97% e.e.) > ethylketones (74-88% e.e.)]. Almost complete reagent control was obtained in the additions of thioester enolates to protected lactic aldehyde (thiopropionate addition: desired diastereomer ≥ 99%; thioacetate addition: desired diastereomer 93-94%) and protected glyceraldehyde (thiopropionate: 95-99%; thioacetate 96-97%). The results were slightly worse with α-methyl-β-benzyloxypropionaldehyde (thiopropionate 65-95%; thioacetate 68-96%)[7].

Additions to *N*,*N*-dibenzylamino aldehydes were also highly diastereoselective: the chiral boron enolate of *t*-butylthioacetate derived from ent-**7** was able to overcome the inherent substrate preference for the Felkin-type product (3,4-*anti*) observed with achiral enolates. It is worth noting that in the "matched" cases the 3,4-*anti*: 3,4-*syn* diastereomeric ratios are ≥ 98.2:1.8, while in the "mismatched" cases the 3,4-*syn*: 3,4-*anti* ratios are ≥ 95.4:4.6. These results indicate that it is possible to obtain either the 3,4-*anti* or the 3,4-*syn* adduct with very high diastereoselectivity by simple variation of

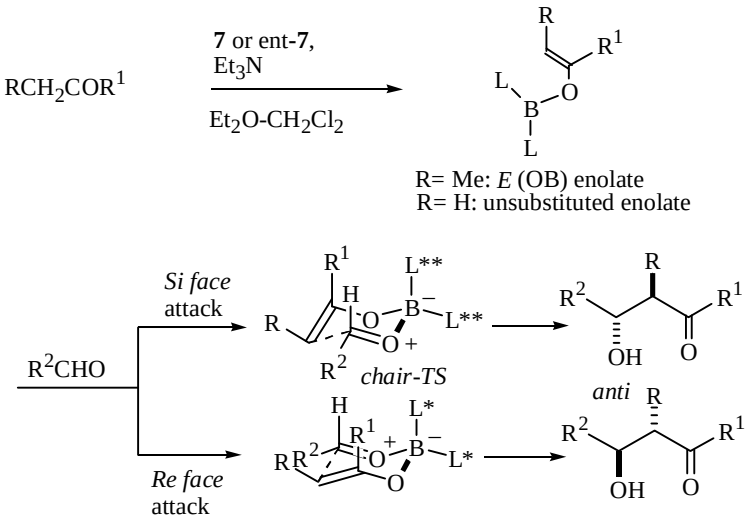


Figure 4. The aldol reactions using menthone-derived reagents. L* derived from (-)-menthone. L** derived from (+)-menthone.

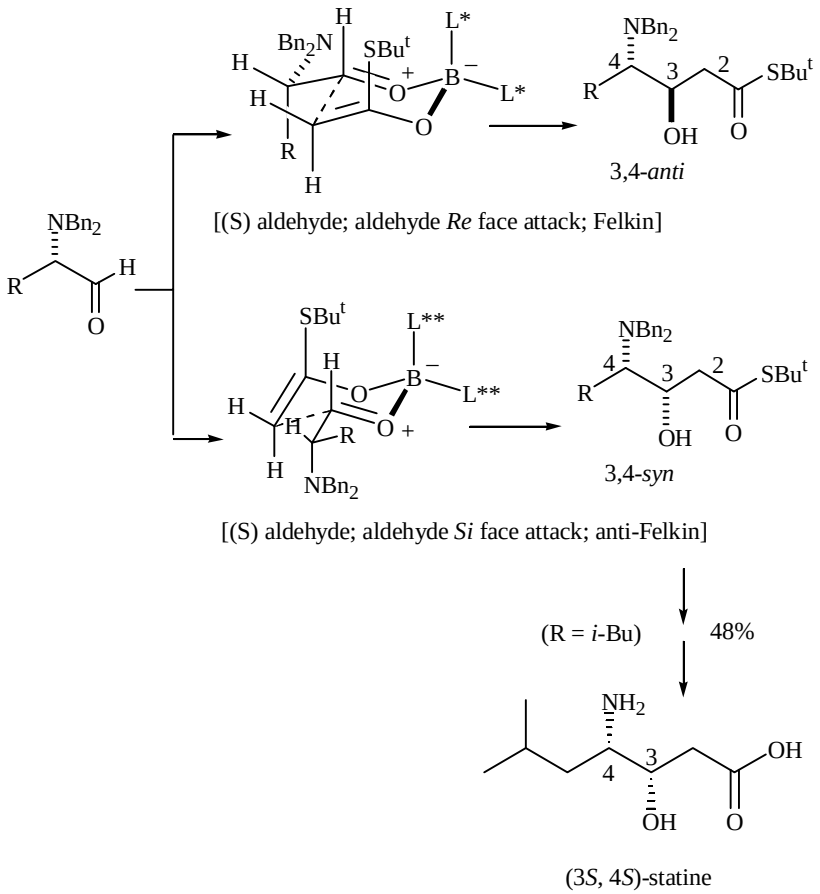


Figure 5. Reagent controlled additions to α-amino aldehydes. L* derived from (-)-menthone. L** derived from (+)-menthone.

the chiral boron ligand configuration [L* derived from (-)-menthone, L** from (+)-menthone; Fig. 5][8]. (3*S*, 4*S*)-Statine, the main component of the specific aspartic protease inhibitor pepstatine, was synthesized in a few steps starting from *L*-leucine (Fig. 5)[8].

Chiral Boron Enolates Derived from α-halosubstituted Thioacetates

We have recently reported that the enolates derived from α-halo thioacetates (X = Cl, Br) and the chiral boron reagent **7** or ent-**7** (Fig. 6)[9] react with aldehydes to give α-halo-β-hydroxy derivatives with high diastereo- (*anti:syn* 91:9 - > 99:1) and enantiocontrol (e.e. = 94 - > 98%). *Anti* α-halo-β-hydroxy thioesters were transformed in high yield into β-hydroxy thioesters **8** (Zn/NH_4Cl/MeOH) or into *trans* glycidic thioesters **9** (^{t}BuOK/^{t}BuOH).

The addition of the chiral boron enolates derived from *tert*-butyl α-halothioacetate (X = Cl, Br) to achiral silyl imines leads to α-halo-β-amino thioesters. *N*-trimethylsilylimines were reacted with the *E*(OB) enolate [L** derived from (+)-menthone] to form α-halo-β-amino thioesters, which were isolated in 77-89% yield as hydrochloride salts **10** (Fig.7)[10]. The diastereoselectivity of the reaction (*syn: anti* 92:8 - ≥ 99:1) and the enantiomeric ratios of the major *syn* products (97:3 - ≥ 99.5:0.5) are high, particularly for X = Br (*syn:anti* ≥ 99:1; e.e. ≥ 97%). Simple reduction with $LiAlH_4$ of the α-halo-β-amino thioesters **10** gave non protected *cis* chiral aziridine alcohols **11**. Aziridine (**11b**) is a key intermediate for the synthesis of the broad spectrum, antibacterial, synthetic antibiotics (+)-thiamphenicol and (-)-florfenicol[11].

It is interesting to note that the stereochemistry of the imine (*trans*) determines the *syn* stereochemical relationship in the aldol product **10**. In fact, the absolute configuration of **10** is consistent with a chair transition structure featuring preferential attack on the imine *Re* face (Ar axial, Fig. 7). We may also point out that in the aldehyde case, the R group can adopt an equatorial position (aldehyde *Si* face attack) which eventually leads to the *anti* relationship between the hydroxy and the halogen groups (Fig. 6).

Chiral Boron Enolates Derived from α-oxysubstituted Thioacetates

Our chiral glycolate enolates are able to impart excellent diastereo- (*anti-syn* ≥ 97:3) and enantiocontrol (e.e. =

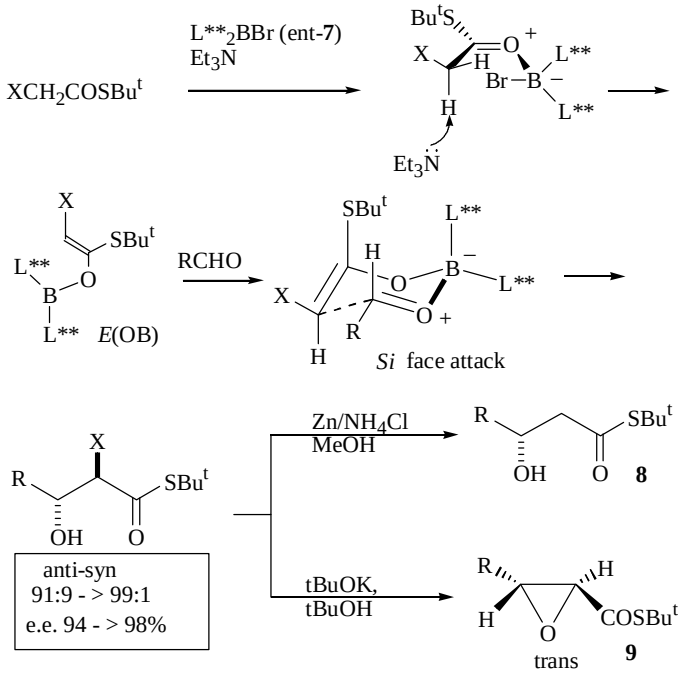


Figure 6. Additions of α-haloacetates to aldehydes. L** derived from (+)-menthone.

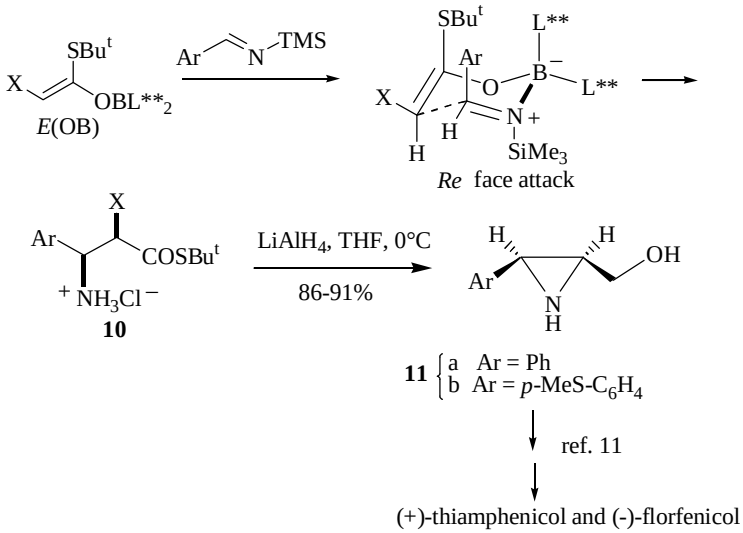


Figure 7. Additions of α-haloacetates to *N*-trimethylsilylimines. L** derived from (+)-menthone.

94-97 %), see Fig. 8[9]. The following is noteworthy: a) the enolization preferentially results in the formation of *E* (OB)-enolates, as implied from the high *anti-syn* ratios observed in the aldol products; b) the enantiomeric and the *anti-syn* ratios are independent of the type of R^1 and R^2 substituents (R^1 = TBDMS, Bn; R^2 = Ph, Bu^t); c) the absolute configuration of the aldol products is consistent with chair transition structures featuring preferential attack on the aldehyde *Re* face [L* derived from (-) menthone].

Semisynthesis of Paclitaxel (Taxol®)

Paclitaxel (**12**) is considered the most promising cancer chemotherapeutic agent and has recently been approved for treatment of metastatic ovarian and breast cancer[12]. Central to all synthetic strategies for paclitaxel is the synthesis and attachment of the C-13 side chain to the baccatin III nucleous, since the presence of this side chain has proven to be essential for the biological activity of paclitaxel. The chemical complexity of paclitaxel dictates that its commercial production by total synthesis is not likely to be economical, while the naturally derived 10-deacetylbaccatin

III (**13a**, Fig. 9) is readily available in relatively high yield from the needles of the European Yew *T. baccata*. Preparation of quantities of paclitaxel economically by a semisynthetic approach which involves the condensation of protected 10-deacetylbaccatin III (**13b,c**) with suitably protected *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine (**14**), provides

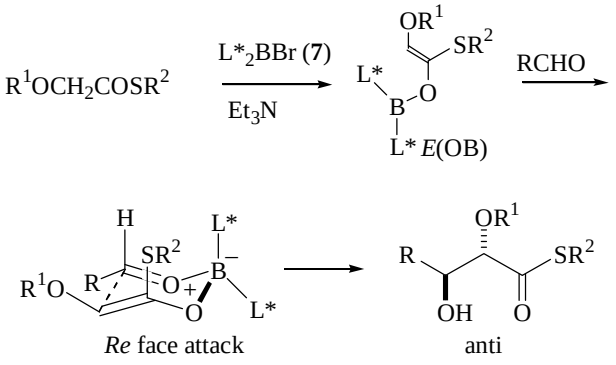
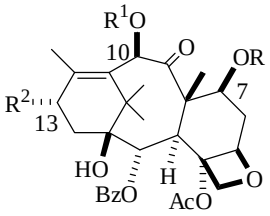


Figure 8. Additions of α-oxyacetates to aldehydes. L* derived from (-)-menthone.



(**12**) R = H; R^1 = -$COCH_3$; R^2 = **14**
(**13a**) R = R^1 = H; R^2 = OH
(**13b**) R = -$SiEt_3$; R^1 = -$COCH_3$; R^2 = OH
(**13c**) R = R^1 = -CO-OCH_2CCl_3; R^2 = OH

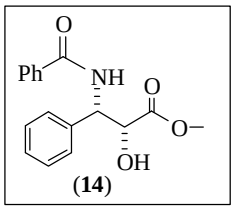


Figure 9. Paclitaxel (**12**), free (**13a**) and protected (**13b,c**) 10-deacetylbaccatin III, *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine (**14**).

an alternative source of this important natural product and the access to semisynthetic analogs.

We have developed a very simple, new and straightforward approach to the paclitaxel side chain using the imine addition reaction of thioester derived boron enolates bearing chiral ligands.[13,14] The side chain is assembled in one single step with the correct relative (*syn*) and absolute stereochemistry (2*R*, 3*S*). The desired compound (**16**) was isolated practically pure by simple solvent extraction without the need for chromatography (Fig. 10). The overall yield is 60% (starting from **15**), and the stereochemical control is high (*syn:anti* ≥ 96:4; e.e. ≥ 96%). Oxazolidine formation occurs using 2-methoxypropene and pyridinium toluene-4-sulfonate in toluene to give (**17**) (≥ 90%) and the small amount of the unwanted *anti* diastereomer is removed in this step via chromatography (the *anti* compound does not cyclize under these conditions).

Following a different approach, the desired compound (**19**) was obtained in an overall yield of 71% (starting from **18**), with an *anti:syn* ratio ≥ 97:3, and ≥ 95% enantiomeric purity (Fig. 11)[13,14]. Compound **19** was then treated with aqueous HF in acetonitrile, and the resulting crude compound **20** (100%, *anti:syn* 97:3) was cyclized using thionyl chloride in refluxing 1,2-dichloroethane.

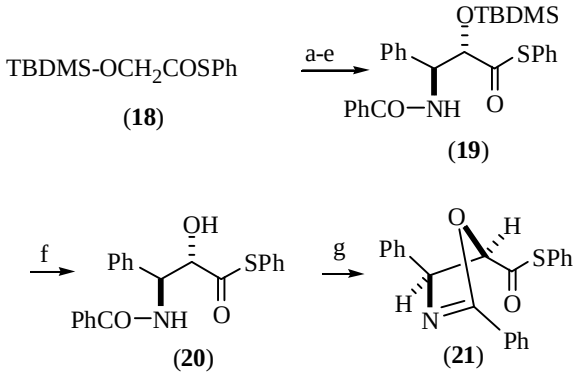


Figure 11. a) L*2BBr (**7**) derived from (-)-menthone, Et_3N, CH_2Cl_2, Et_2O, 0 °C to RT, 5 h; b) PhCH=NSiMe_3, -78 °C to -5 °C; c) pH 7 phosphate buffer quenching, CH_2Cl_2 extraction, evaporation; d) 0.25 N HCl in MeOH:H_2O 1:1 (v:v), RT; evaporation; e) PhCOCl, Et_3N, CH_2Cl_2, 4-dimethylaminopyridine, 0 °C; work-up and chromatography (71% yield over steps a-e); f) HF, CH_3CN, H_2O, 100%; g) $SOCl_2$, $CHCl_3$, 45 °C; 1,2-dichloroethane, 100 °C, 65%.

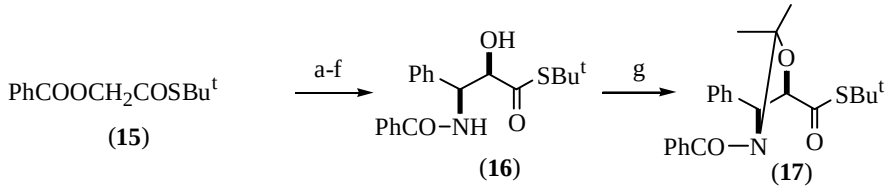


Figure 10. a) L**2BBr (ent-**7**) derived from (+)-menthone, Et_3N, CH_2Cl_2, Et_2O, -25 °C, 7 h; b) PhCH=NSiMe_3, -78 °C to -5 °C; c) pH 6 phosphate buffer quenching, CH_2Cl_2 extraction, evaporation; d) 1:1 (v:v) MeOH: 1 N aqueous HCl, RT; evaporation; e) solid washed with Et_2O; f) pH 8 aqueous phosphate buffer, MeOH, RT; CH_2Cl_2 extraction (60% yield over steps a-f); g) CH_2=C(OMe)Me, pyridinium toluene-4-sulfonate, toluene, 80 °C, ≥90%.

Oxazoline formation occurred with complete inversion of sterochemistry at the C-2 stereocenter to give (**21**) (65% yield), and the traces of the unwanted *syn* diastereomer were removed in this step via chromatography (the *syn* compound does not cyclize under these conditions). Thioesters **17** and **21** were attached directly to the baccatin nucleous. By treatment of a mixture of protected baccatin III [7-TES,10-Ac (**13b**) or 7,10-di-Troc (**13c**)] and oxazolidine (**17**) or oxazoline (**21**) in THF at 0 °C with $LiN(SiMe_3)_2$, the 13-O acylated compounds were obtained in high conversion and yield (74-75% from **17** and 89-90% from **21**). The 13-O acylated compounds were deprotected to give paclitaxel (**12**) in high yields[13,14].

From the above results, and from many other not reported, it is clear that the stereochemical outcome of the aldol additions to imines is strongly dependent on the type of thioester used (COSPh *vs.* $COSBu^t$), contrary to the results using the same boron reagents and aldehydes (Fig. 8)[9], while the role of the oxygen protecting group is relatively minor. The stereochemical outcome can be rationalized using chair vs. boat transition structures (Fig. 12). *Ab initio* MO calculations (3-21G basis set) featuring the addition of the BH_2 enol borinate derived from acetaldehyde to formaldehyde-imine have recently shown that two competing cyclic transition structures are likely to be important: the chair and the boat[15].

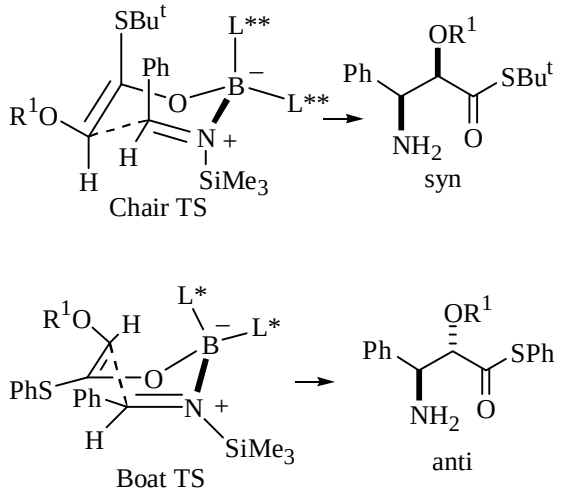


Figure 12. Transition states for the enolate additions to imines. L* derived from (-)-menthone. L** derived from (+)-menthone.

Enantioselective Aldol Chemistry on Solid Phase

Studies of organic synthesis on a solid support have witnessed an explosive surge of interest in the last few years. Much effort has been expended in the adaptation to the solid phase of the synthetic armoury of organic chemistry. Solid supported strategies leading to the iterative synthesis of the most important biopolymers, namely peptides, oligosaccharides, and oligonucleotides are well established and have also been adapted to automation. However, a solid phase approach to polyketides, a class of biopolymers consisting of a 1, 3, 5, n-polyol chain with defined stereochemistry, has not yet been demonstrated.

Two different approaches, in principle, could be employed for solid phase supported aldol chemistry: formation of the enolate linked to the resin and reaction with an aldehyde in solution; or the immobilization of the aldehyde on the solid support and treatment with an enolate in solution. The second synthetic pathway allows for possible iteration of the aldol process towards a solid phase synthesis of polyketide-type structures, provided a conversion to another aldehyde is accomplished.

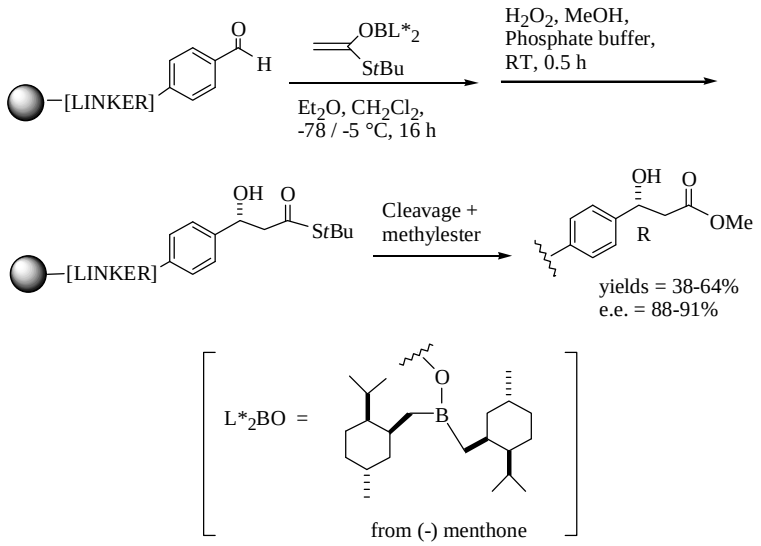


Figure 13. Solid phase aldol reaction scheme.

We were attracted by the possibility of developing a stereoselective aldol protocol on solid phase bound aldehydes using our thioester-derived chiral enolborinates bearing chiral ligands. These boron enolates have been shown to impart a strong reagent control in their reactions with chiral aldehydes (see above), which is required in order to control stereochemistry of the growing chain. Furthermore, the use of thioesters should enable easy conversion to the aldehyde for iteration.

Enantioselective addition reactions of the chiral boron enolate derived from thioacetate to solid phase bound aldehydes have successfully been carried out with a variety of aldehydes and linkers, and giving rise to aldol products in yields and enantioselectivities comparable to the usual solution conditions (Fig. 13)[16].

Acknowledgments

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3. It is more convenient to use the same stereodescriptors for the boron enolates derived from different substrates. As sequence-rule-priority changes passing from ketones (OB > alkyl) to esters (OB < O-alkyl) to thioesters (OB < S-alkyl), we define the enolates as *Z*(OB) or *E*(OB)-enolates, conventionally attributing to the OB substituent the highest priority.
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