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Asymmetric synthesis of protected α-alkyl-β-amino-δ-hydroxy esters by stereocontrolled elaboration of THYM*

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Abstract

Highly diastereoselective internal Michael addition of the carbamate moiety of enoate **1b** [derived from asymmetrized tris(hydroxymethyl)methane (THYM*)] leads to oxazinone **4**, which can, in turn, be alkylated with moderate to good diastereoselectivity in the position α to the ester moiety to give protected *anti,anti* α-alkyl-β-amino-δ-hydroxy esters.

Keywords: intramolecular Michael-type amination; α-alkylation of esters.

β-Amino acids are very valuable compounds: not only do they constitute one of the more obvious starting materials to β-lactams, but also some of them have pharmaceutical properties or are part of peptides acting as enzymatic inhibitors or as antitumor agents.[1] Several methods are known for the synthesis of β-amino acids, and most of these can also be applied to the synthesis of non–racemic products. Among them, the Michael addition of an *N*-nucleophile to an α,β-unsaturated ester is widely used,[1] with the chirality placed either in the nucleophile[2,3] or in the unsaturated ester,[4] or in both.[5] Tandem or sequential electrophilic attack at the α-carbon has also been studied and further functionalized β-amino esters[1–5] have been successfully achieved.

While, to our knowledge, the intermolecular addition of lithium salts of acylamides to α,β-unsaturated esters has not been reported, the intramolecular process, involving an allylic or homoallylic carbamate moiety is well known.[6–8]

Taking advantage of the synthetic opportunities offered by asymmetrized tris(hydroxymethyl)methane THYM*, a highly versatile chiral building block recently introduced by us and utilized in many asymmetric syntheses,[9] we planned to use this unit as the starting material for synthesizing some branched β-amino-δ-hydroxyacids and their α-alkylated derivatives.

To this purpose, we prepared the α,β-unsaturated *t*-butyl[10] ester (*R*)-**1a** (*E*:*Z* ratio=9:1), starting from THYM* via oxidation to the corresponding aldehyde and subsequent Wittig olefination,[9] and, as a first

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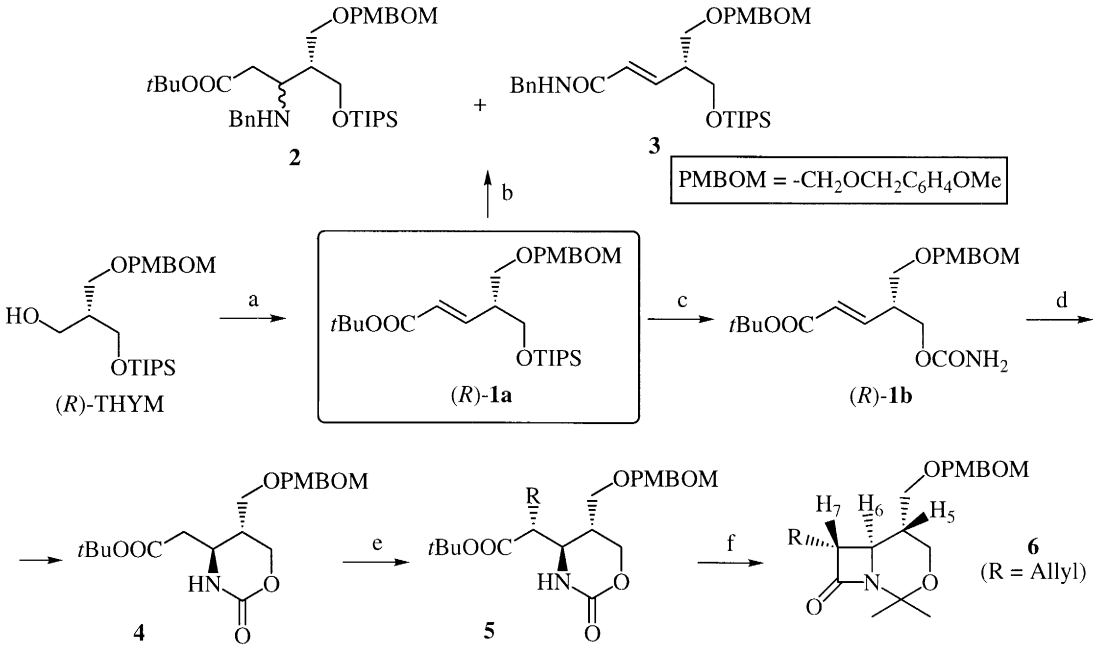
approach, we studied that addition of the achiral lithium *N*-benzyltrimethylsilylamide (LSA)[11] (Scheme 1). This silylated amine was chosen taking into account the good chemical and stereochemical results generally obtained when using this nucleophile in similar Michael-type additions.[4,11] Unfortunately, in our case, the outcome was rather discouraging: not only was **2** isolated in rather low chemical yield (not exceeding 35% when the reaction was run in THF), but also, even at low temperature (−78°C), the stereochemical control on **1a** was disappointingly poor [the diastereoisomeric ratio of **2** was about 3:2 in favour of the less polar (TLC) isomer] and quite large amounts of amide **3** (derived from 1,2- instead of 1,4-attack) were detected, notwithstanding use of the *t*-butyl ester. Also, a deconjugated β,γ-unsaturated ester (derived from deprotonation at the γ position of **1a**) was formed,[11] along with by-products from the protecting group removal.

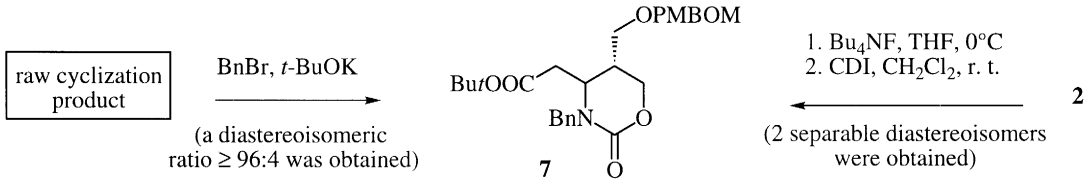


Scheme 1. (a) (i) $(COCl)_2$, DMSO, *i*-Pr_2NH, 92%; (ii) $Ph_3P{=}CHCO_2Bu^t$, 92% (two steps); (b) Bn(TMS)NLi, THF, −78°C; (c) Bu_4NF, 80%; $ClSO_2NCO$, then H_2O, 85%; (d) *t*-BuOK (see text); (e) base, RX (see Table 1); (f) (i) Boc_2O, Et_3N, DMAP, CH_2Cl_2, 94%; (ii) Cs_2CO_3, MeOH, 88%; (iii) KOH, EtOH, 77%; (iv) TIPS–Cl, DBU, MeCN, 59%; (v) $(PyS)_2$, PPh_3, MeCN, 90%; (vi) TBAF, THF, 44%; (vii) DME, $BF_3 \cdot Et_2O$, CH_2Cl_2, 39%

Since better results, especially in terms of asymmetric induction, could reasonably be expected from an intramolecular process, we turned to the synthesis of alkene (*R*)-**1b**, following already known standard procedures[7,12] (Scheme 1). A perusal of literature data regarding the intramolecular addition of homoallylic *O*-carbamates to α,β-unsaturated esters having stereocentres at both the γ- and the δ-carbon, indicates that diastereoselectivity mainly depends on the chirality of γ-carbon (1,2-*anti* induction predominates) when an oxygenated functional group is present at the γ-carbon itself.[7] On the contrary, when a fluorine is present at the γ-carbon, the stereochemistry of the newly formed chiral carbon seems to depend only on the chirality of the δ-carbon (1,3-*syn* induction predominates).[8] Although cyclization of homoallylic carbamates having chirality only at the δ-carbon are known,[7a] to the best of our knowledge no example has been reported on homoallylic carbamates having chirality only at the γ-carbon, such as **1b**.

Base-induced cyclization of (*R*)-**1b** was at first assayed using *t*-BuOK as a base, in THF for 20 min

at 0°C,[7e] which afforded the oxazinone **4** with 59% chemical yield. With the aim of improving this result, we examined the effect of various parameters: base, temperature, reaction time. While oxazinone **4** was reasonably stable under the reaction conditions, a major problem arises from the base-sensitivity of substrate **1b**. Potassium *t*-butoxide seemed to be the base of choice, notwithstanding the claimed little importance of employed base,[7a] and a compromise between a lower temperature and extended reaction time was used in order to suppress undesirable side reactions. Finally, 70% of purified **4** was obtained when the reaction was run in THF, using a slight excess of base (*t*-BuOK) for 3 h at −50°C. TLC analysis using a variety of eluents and ^{1}H and ^{13}C NMR spectra indicated that **4** was present in only one diastereomeric form,[13] with *trans* relative configuration[14] of the two substituents. As a further confirmation of this result, we benzylated the raw product of cycloaddition to achieve the *N*-benzylated derivative **7**, both diastereomeric forms of which being available starting from amino ester **2**: only a trace (≤4%) of the *cis*-diastereomer could be detected (Scheme 2).



Scheme 2.

Table 1
Alkylation of doubly deprotonated **4**

Entry	Base (eq)[a]	Temp. and time for deprotonation	RX (eq)	Temp. and time for alkylation	Yield of 5 [%][b] (diast. ratio)
1[c]	LiHMDS (2.1)	-78°C, 50 min	MeI (1.1)	-78°C, 40 min	38 [53] (64 : 36)
2[d]	**LiHMDS (2.1)**	**-**	**MeI (1.1)**	**-78°C, 90 min**	**77 [88] (67 : 33)**
3[d]	LiHMDS (2.1)	-	MeI (5.0)	-78°C, 90 min	5 [50] (63 : 37)
4[d]	LiHMDS (2.2)	-	Allyl-Br (1.1)	-78°C, 90 min	41 [61]
5[d]	**LiHMDS (2.2)**	**-**	**Allyl-Br (10)**	**-78°C, 90 min**	**83 (95 : 5)**
6[d]	**LiHMDS (2.2)**	**-**	**BnBr (10)**	**-78°C, 90 min**	**76 [85] (96 : 4)**

[a] Every reaction was run in dry THF under an inert (N_2) atmosphere. [b] Yields based on unrecovered **4** are reported in brackets. Diastereoisomeric ratios were determined by ^{1}N NMR spectra. [c] Order of mixing: substrate + base + RX. [d] Order of mixing: substrate + RX + base.

With the protected β-amino ester in hand, we turned our attention to its elaboration. Herein, we report the results of alkylation in the α-position with respect to the ester moiety (Scheme 1).

The reaction with methyl iodide was chosen as a probe in order to find best alkylation conditions: some selected results are reported in Table 1. Using lithium diisopropylamide (LDA) as a base[15] to doubly deprotonate **4**, resulted in decomposition of substrate, accompanied by only traces of the *N*-methylated product. On the contrary, LiHMDS as a base furnished the desired product, in yields depending on the time of alkylation and on the order of mixing of reagents. An excess of alkylating agent is deleterious, probably due to a side reaction between methyl iodide and LiHMDS, and added hexamethylphosphoric

amide (HMPA)[16] or lithium chloride[15] had no beneficial effect. The conditions of choice involved premixing the substrate with about an equivalent of MeI and then adding a slight (5–10%) excess of base (entry 2); diastereoisomeric excess is about 35%.

Other alkylating agents were then tested and in some cases they gave both satisfactory chemical and stereochemical yields (entries 5 and 6 of Table 1, diastereoisomeric excess ≥90%). As for the methylation reaction, the conditions of choice were always addition of base (LiHMDS) to a mixture of substrate, but an excess of alkylating agent had to be employed, in order to improve the chemical yields (cf. entries 4 and 5). Different order of addition and different bases (LDA, KHMDS)[16] gave worse results.[17]

On the basis of the coupling constant values ($J_{H\text{-}6/H\text{-}7}$=1.5 Hz and $J_{H\text{-}5/H\text{-}6}$=9.9 Hz) of the β-lactam **6**, obtained from **5** after deblocking and successive cyclization (see Scheme 1), the relative configuration of the two stereocentres, in the main diastereomer of **5**, was established to be *anti*,*anti* by comparison with literature data.[18]

Reaction with other electrophiles, as well as further elaboration of **5**, will be reported in a forthcoming paper.

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13. For an α,β-unsaturated ester of *E* configuration, this is quite a notable result (see Ref. 7d).
14. The relative configuration of C-4 and C-5 in the oxazinone ring was established to be *trans*, after many unsuccessful efforts (coupling constant $J_{H\text{-}4/H\text{-}5}$ of **4** could not be determined, even with double resonance experiments), by transforming **4** into acetate **I** [(i) MeI, *t*-BuOH, −30°C; (ii) DDQ, *t*-BuOH, CH_2Cl_2, rt; (iii) Ac_2O, pyridine, 0°C], which showed $J_{H\text{-}4/H\text{-}5}$ about 1.5 Hz and $J_{H\text{-}5/H\text{-}6}$ and $J_{H\text{-}5/H\text{-}6'}$ 1.5 and 3.3 Hz, respectively [see: (a) Bando, T.; Harayama, H.; Fukazawa, Y.; Shiro, M.;

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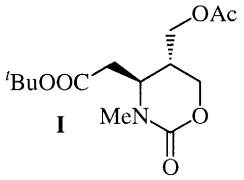

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17. Some selected analytical data for compounds **1a**,**b** and **4** are here reported (optical rotatory powers are taken at 22°C in $CHCl_3$, ^{1}H NMR spectra in $CDCl_3$). Compound (*R*)-(*E*)-**1a**: $[\alpha]_D$=+1.2 (*c* 0.94); ^{1}H NMR: 1.04–1.09 [m, 21H, (Me_2CH)$_3$Si], 1.47 (s, 9H, Me_3C), 2.55–2.75 (m, 1H, C*H*CH_2OPMBOM), 3.65–3.80 (m, 4H, CH_2OPMBOM and CH_2OSi), 4.52 (s, 2H, OCH_2Ar), 4.72 (s, 2H, OCH_2O), 5.86 (dd, *J*=15.8 and 1.0, 1H, Bu^{t}OCOC*H*=), 6.87 (dd, *J* =5.8 and 8.3, 1H, CHC*H*=), 6.86–6.90 (m, 2H) and 7.25–7.29 (m, 2H) (Ar*H*). Compound (*R*)-(*E*)-**1b**: $[\alpha]_D$=−3.8 (*c* 0.98); ^{1}H NMR: 1.48 (s, 9H, Me_3C), 2.75–2.91 (m, 1H, C*H*CH_2OCO), 3.65 (d, *J*=5.9, 2H, CH_2OPMBOM), 3.81 (s, 3H, *Me*O), 4.19 (app. dd, *J*=6.2 and 2.1, 2H, CH_2OCONH$_2$), 4.52 (s, 2H, CH_2Ar), 4.6 (broad s, 2H, NH_2), 4.72 (s, 2H, OCH_2O), 5.89 (dd, *J*=15.8 and 1.2, 1H, Bu^{t}OCOC*H*=), 6.81 (dd, *J*=15.8 and 7.7, 1H, CHC*H*=), 6.86–6.92 (m, 2H) and 7.25–7.32 (m, 2H) (Ar*H*). Compound (4*S*, 5*R*)-**4**: $[\alpha]_D$=−37.1 (*c* 2.06); ^{1} H NMR: 1.46 (s, 9H, Me_3C), 1.90–2.04 (m, 1H, C*H*CHNH), 2.43 and 2.59 (AB part of an ABX system, J_{AB}=16.9, J_{AX}=10.4, J_{BX}=2.9, 2H, CH_2OCO$_2$Bu^t), 3.60 and 3.62 (AB part of an ABX system, J_{AB}=10.4, J_{AX}=9.1, J_{BX}=3.6, 2H, CH_2OPMBOM), 3.68–3.81 (m, 1H, C*H*NH), 3.81 (s, 3H, *Me*O), 4.19 and 4.28 (AB part of an ABX system, J_{AB}=11.4, J_{AX}=7.5, J_{BX}=3.6, 2H, CH_2OCONH), 4.52 (s, 2H, CH_2Ar), 4.72 (s, 2H, OCH_2O), 5.83 (broad s, 1H, N*H*), 6.87–6.92 (m, 2H) and 7.24–7.28 (m, 2H) (Ar*H*). The optical purity of both (*R*)-(*E*)-**1a** and (4*S*, 5*R*)-**4** was checked via NMR spectra of Mosher's esters prepared from alcohols obtained by removing a protecting group from **1a** (TIPS) and **4** (PMBOM) and was found to be comparable with optical purity of starting THYM* (ee≅90%).
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