Pergamon

Tetrahedron Letters 41 (2000) 1737–1740

TETRAHEDRON LETTERS

Asymmetric functionalization of a chiral non-racemic oxazolidine ester enolate. A new route towards the preparation of quaternary serine esters

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Received 25 November 1999; accepted 23 December 1999

Abstract

A new route towards the preparation of enantiomerically pure quaternary serine esters is described. The key step involves the diastereoselective functionalization of an oxazolidine ester enolate having an exocyclic chiral appendage.

The asymmetric synthesis of α-substituted serines has been of major interest in recent years.[1] Such amino acids can be encountered as a part of the bioactive natural products,[2] and can also be precursors of various α,α-disubstituted amino acids.[3]

Several synthetic strategies have been developed in the preparation of these derivatives. Among them, one of the classical approaches is the application of the Seebach's SRS principle (self-regeneration of stereocentres) starting from oxazolidine **1** (Fig. 1).[4] In this approach, the original chirality of serine is transferred to a temporary centre of chirality, which will control the diastereoselective formation of the quaternary centre. The nature of the nitrogen-protective group was reported to have a strong influence on the course of the reaction, the *N*-formyl derivative leading to the most stable lithium enolate. However, a very efficient aldol reaction was reported by Corey and Li in the lactacystin synthesis, using *N*-benzyl oxazolidine **2** as starting material.[5] We therefore decided to investigate the alkylation of oxazolidine **3**, including a 'chiral *N*-benzyl'-protective group, in order to study the chirality transfer in such a system having an exocyclic chiral appendage.

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0040-4039/00/$ - see front matter
PII: S0040-4039(00)00026-5

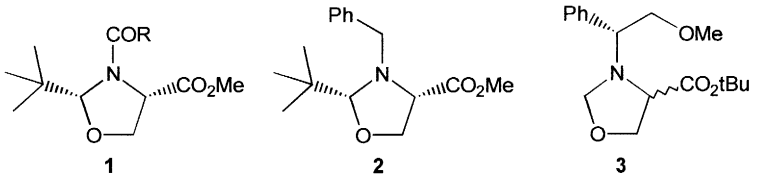
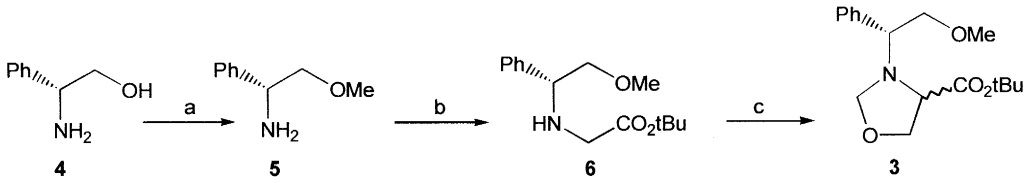


Fig. 1.

Compound **3** can be efficiently prepared as a 1/1 diastereomeric mixture in three steps on a multigram scale, as depicted in Scheme 1. The key step is the oxazolidine ring system formation through a 3+2 dipolar cycloaddition with paraformaldehyde.[6]

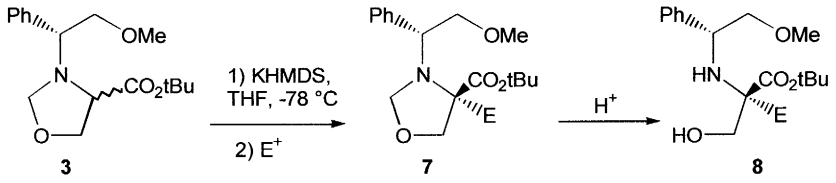


Scheme 1. *Reagents and conditions:* (a) (i) KH, THF; (ii) MeI, 77%; (b) $BrCH_2CO_2tBu$, K_2CO_3, MeCN, 73%; (c) $(CH_2O)_n$ toluene, Δ, 87%

After optimization, potassium hexamethylsilylamide proved to be the most convenient base for enolate generation. Contrary to what was reported with oxazolidines **1** and **2**, no additive (HMPA, DMPU or LiBr) was required to improve the yields by lowering competitive β-elimination rate.[7]

The reactivity of the potassium enolate was then investigated with several electrophiles. Best results were obtained with iodide as a leaving group for alkylating reagents. The use of chlorinated or brominated derivatives led to the same product, but in a lower yield. In all cases, the reaction proved to be highly stereoselective (Table 1).[8]

Table 1

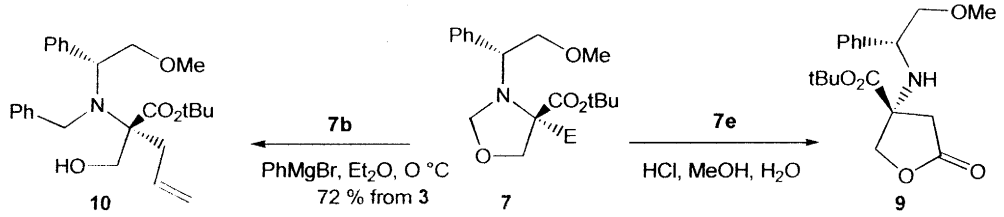


E^+	compound	d.e. (%)[a]	Yield (%)[b]	compound	H^+	Yield (%)[c]
MeI	**7a**	> 95	-	**8a**	HCl, MeOH, H_2O	63
CH_2CHCH_2I	**7b**	86	97	**8b**	HCOOH, H_2O, THF	54
$PhCH_2I$	**7c**	88		**8c**	HCl, MeOH, H_2O	61
PhCOCl	**7d**	81	73			
$BrCH_2CO_2Me$	**7e**	> 95		**9**	HCl, MeOH, H_2O	29

a) Determined by ^1H NMR analysis of the crude reaction mixture. b) Isolated yield. c) Overall yield of diastereomerically pure material from **3**

In some cases, compounds **7** were not very stable, and the crude reaction mixture was directly submitted to acidic hydrolysis to furnish amino esters **8**. Selective oxazolidine cleavage needed careful optimization because of the presence of acid sensitive quaternary *t*-butyl ester. If needed, minor diastereomer could be discarded at this stage by column chromatography and/or crystallization.

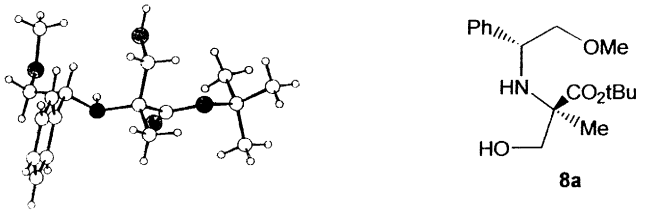
Hydrolysis of compound **7e** did not lead to **8** but to lactone **9** (Scheme 2). The low overall yield, caused by the presence of acidic protons in the electrophile, is still to be optimized.



Scheme 2.

An alternative protective group transformation, based on the reactivity of oxazolidines as potential iminiums, was performed on compound **7b**, leading to *N*-benzyl amino ester **10** (Scheme 2).

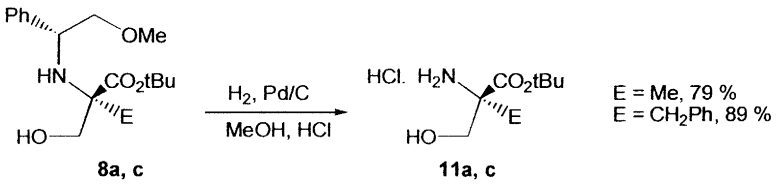
The absolute configuration of the newly created asymmetric centre was determined by X-ray analysis of the crystalline methyl derivative **8a** (Fig. 2).[9] Alkylation occurred on the *Si* face of the transient enolate.



X ray structure of compound **8a**

Fig. 2.

Finally, compounds **8a** and **8c** were deprotected by hydrogenolysis to give **11a** and **11c** in 79 and 89% yield, respectively (Scheme 3).



Scheme 3.

In conclusion, oxazolidine **3** proved to be a suitable tool for the elaboration of enantiopure α-substituted serine esters. Formation of the quaternary centre proceeds efficiently, in good yield and with good diastereoselectivity. Applications of this method to the synthesis of natural products as well as aldol reactions are currently under investigation and will be reported in due course.

Acknowledgements

One of us (V.A.) thanks the MENRT for a grant.

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5. For a recent review, see: Corey, E. J.; Li, W.-D. Z. *Chem. Pharm. Bull.* **1999**, *47*, 1–10.
6. Bureau, R.; Mortier, J.; Joucla, M. *Bull. Soc. Chim. Fr*. **1993**, *130*, 584–596. Toluene has to be degassed prior to reflux to avoid formation of ca. 10% *N*-methylation.
7. For a general discussion on β-elimination with oxazolidine esters, see Ref. 4a.
8. Typical procedure: To a solution of the diastereomeric mixture of oxazolidine **3** (200 mg, 0.65 mmol) in dry THF (5 mL) at −78°C under argon atmosphere was added KHMDS (0.5 M in toluene, 2.60 mL, 1.30 mmol) by cannula. After 0.5 h, iodomethane (122 μL, 1.95 mmol) was added. The reaction mixture was stirred at −78°C for 2.5 h and then quenched with saturated NH_4Cl aqueous solution (5 mL). The mixture was allowed to warm to room temperature and diluted with Et_2O (5 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude product (205 mg) was dissolved in a mixture of MeOH (2.5 mL) and H_2O (5 mL). An aqueous solution of HCl (1 M) was added until pH=2. The reaction was stirred for 6 h at room temperature and quenched with saturated K_2CO_3 solution until pH=8. After addition of Et_2O (5 mL), the aqueous layer was separated and extracted with two 10 mL portions of CH_2Cl_2; the combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude mixture was purified by flash chromatography on silica gel (cyclohexane:AcOEt, 80:20) to give the pure compound **8a** (126 mg, 0.41 mmol, 63% overall yield).
9. Compound **8a**. Small colourless crystal (0.20×0.30×0.30 mm) recrystallized from heptane. $C_{17}H_{27}NO_4$, M_w=309.40, mp=104°C. Orthorhombic system, space group $P2_12_12_1$, Z=4, a=10.668 (5), b=12.397 (6), c=13.436 (6) Å, V=1777(1) Å^3, d_c=1.157 g cm^{-3}, F(000)=672, λ (CuKα)=1.5418 Å, μ=0.66 mm^{-1}; 1858 diffractometric data measured (Nonius CAD-4 diffractometer), 1858 unique, of which 1482 considered as observed with $I \geq 2.0\sigma(I)$; absorption ignored. The structure was solved by direct methods using the SHELXS86 program and refined by full-matrix least-squares based upon unique Fo^2 with the SHELXL93 program. Refinement converged to $R_1(F)$=0.0708 (for the 1482 observed Fo) and $wR_2(F^2)$=0.2078 (for all the 1858 data with goodness-of-fit S=1.079). In the final difference map, the residual electron density was found to be between −0.33 and 0.28 eÅ^{-3}. Lists of the fractional atomic coordinates, thermal parameters, distances, bond and torsion angles have been deposited at the Cambridge Crystallographic Data Centre, UK, as Supplementary Material (CIF file).