Stereoselective Synthesis of (4S,5S)-5-Vinylloxazolidin-2-one-4-carboxylate as a β-Vinylserine Synthetic Equivalent by Vinyl Grignard Addition to an N-Tosyl Version of Garner’s Aldehyde

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Abstract A highly efficient synthesis of a β-vinylserine synthetic equivalent is reported that exploits the stereodirecting effect of the N-toluenesulfonamide in an anti-diastereoselective (8.5:1) vinyl Grignard addition to an analogue of Garner’s aldehyde. Both aryl and alkyl Grignards are shown to give increased anti-selectivity compared with N-Boc Garner’s aldehyde.

Key words vinylserine, alkyl amino acid, Garner aldehyde, oxazolidinones

As part of our synthetic work directed toward glycopeptide mimetics, we required a suitably protected (25S,3S)-β-vinylserine (β-VSer) for use as a synthetic building block. Many noncanonical amino acids have been incorporated into protein and peptide structures to interrogate various cellular functions. In particular, alkyl amino acids incorporated into peptides have proven to be useful for peptide stapling by a cross-metathesis reaction to afford conformationally restricted peptidomimetics. In addition, Zhang and van der Donk have examined the effect of direct alkyl amino acid incorporation. They incorporated a diastereomer of our desired β-VSer (referred to as a threonine analogue) into a peptide sequence of lacticin synthetase to examine substrate selectivity toward dehydration reactions. The pentenolic backbone of β-VSer itself is also a common scaffold for dipeptide isosteres, which have been investigated as enzyme inhibitors and as receptor antagonists. This platform has also been a versatile synthetic intermediate for preparing spingomyelin analogues and glycosidase inhibitors such as the deoxynojirimycins. It has also served as a building block for antitumor agents such as 2-epi-pa-chastrissamine or for glycopeptide and β-lactam antibiotics. For our purposes, we sought to elaborate the β-VSer alkene through cross-metathesis and/or Trost–Tsuji π-allylic alkylation chemistry for the development of novel glycopeptides.

Given the versatility and interest in this simple building block, we elected to exploit an oxazolidinone scaffold 1 as a β-VSer synthetic equivalent in which both the amine and the hydroxy functions are simultaneously protected (Scheme 1). Although there are excellent reports on carbamate cyclizations and an allylic C-H amination that yield trans-4,5-disubstituted oxazolidinones stereospecifically, our studies required a cis-oxazolidinone. cis-4,5-Disubstituted oxazolidinones of this sort are known and are commonly derived from anti-2-aminopent-4-en-1,3-diols such as 2.

Both vinyl oxazolidinones and functionalized 2-amino-4-en-1,3-diols are valuable synthetic intermediates that have been used to prepare numerous natural products and medicinal targets, as discussed above. Although synthetic approaches from carbohydrates, azide epoxide openings, and chiral glycin enolate aldols are available, the more common synthetic approaches entailing nucleophilic additions to α-amino-β-hydroxy aldehydes or ketones provide varying degrees of control of stereochemistry (Scheme 2).
A survey of the literature indicated one could proceed by a vinyl Grignard addition onto the well-known d-serine-derived Boc-protected Garner’s aldehyde15 or the OTBS-Boc-serinal 4.7,19 followed by an intramolecular cyclization onto the Boc group to form an oxazolidinone. The Grignard approach has been widely used,7,8,16 but is limited due to the selectivity of the Grignard addition; this led Herold to develop a three-step approach employing trimethylsilyl acetylide additions for improved anti-stereoselectivity.17 Although the tert-butyl(dimethyl)silyl ether substrate 4 gives 5 directly, it results in an undesirable 1:2 anti/syn diastereomeric ratio.7 The typical anti-selectivity for vinyl addition to Garner’s aldehyde is reported to range from 3:116a to 6:1 anti/syn, and experimental details indicate that additional purification by chromatography is necessary. From the Grignard product of Garner’s aldehyde, hydrolysis of the N,O-acetal and selective protection of the primary hydroxy groups is needed, followed by formation of the oxazolidinone by a base-induced intramolecular cyclization onto the tert-butyl carbamate to afford 6.18 In an improvement to these early approaches, the Weinreb amide 7 of a protected d-serine, available in four steps, has been employed to form an enone upon addition of vinylmagnesium bromide; this enone can be stereoselectively reduced with Li(t-BuO)2AlH in ethanol giving 5 with a 10:1 preference toward the anti-diastereomer.19

Here, we report a highly selective alternative approach in which the N-tosylamide 8 is used as a stereoregulating orthogonal protecting group; this approach is complementary to the approaches discussed above.

For our purpose, we had concerns about the N-Boc protecting group due to its potential for neighboring-group participation in our planned synthetic manipulations; we therefore initially desired an N-tosyl protected nitrogen on the oxazolidinone 9. Although one could simply tosylate the known oxazolidinone 6 to give 9, we considered initiating our synthesis with the acyclic silyl-protected N-tosyl-d-ser20 or the N-tosyl equivalent of Garner’s aldehyde.21 Vinyl Grignard additions to N-sulfonyl-protected acyclic amino acids are not usually selective. Literature reports suggest that additions to the aldehydes of TsNH-Ala22 and TsNH-Phe23 give poor diastereoselectivities (2:3 anti/syn and 2:1 with the major isomer not identified, respectively). Given the poor selectivity of additions to acyclic amino aldehydes, we opted to pursue the use of a toluenesulfonamide derivative of Garner’s aldehyde 8. Surprisingly, no Grignard chemistry has been reported on this aldehyde. We found that vinylmagnesium bromide added cleanly to give a >95% yield24 (Scheme 3) and was more selective than the N-Boc-protected Garner’s aldehyde, giving the anti-allylic alcohol 10 with an 8.5:1 dr before chromatography. The use of LiCl as an additive in the vinylmagnesium bromide reaction did not alter the results. Although some trial runs using vinylmagnesium chloride directly did show >10:1 diastereoselectivity, these seemed highly dependent on the commercial source and age of the reagent. Conveniently, no rotamers are observed in the NMR spectra of the tosylamides, unlike the Boc-derivatives, making their interpretation more straightforward; moreover, TLC visualization and chromatographic detection is aided by the UV activity of the aromatic sulfonamide.

The improved diastereoselectivity can be partially explained by examining the LUMO energies of the reactive Felkin–Anh conformations (Scheme 4). With the N-sulfonamide there is a strong preference for the C-NTs bond of 9a to lie perpendicular to the plane defined by the aldehyde carbonyl as opposed to the C–CH2O bond in 9a. The LUMO of 9a is 3.46 kcal mol−1 higher in energy than that of 9b, as determined by ground-state gas-phase DFT calculations using an ω-B97XD hybrid GGA functional. This predicts that nucleophilic approach should favor attack on 9b, leading to the 2,3-anti-product. In contrast, the N-Boc derivative has a smaller LUMO energy difference (2.77 kcal mol−1) between the two Felkin–Anh conformations, so it would not be expected to be as stereoselectively based on this analysis.

The trend favoring the 2,3-anti-diastereomer is also observed for aryl and methyl Grignards, with >7:1 ratios being observed (Table 1). Interestingly, ethyl Grignard also afforded an 8:1 selectivity toward the anti-product, which is a near reversal of the syn-preference observed by Joullié and others.25 The 2,3-syn-selectivity has been suggested to arise from chelation to the Boc carbonyl oxygen.26 Which would
contribute to our observed anti-preference with the less chelation-prone tosylamide. Finally, the allyl Grignard gave poor selectivity in this reaction.

For most of the N-tosyl Grignard products, we observed significant decomposition to the diol or rearrangement to dioxolanes on silica gel chromatography, so for 10, the crude product was always carried forward. Acidic hydrolysis of the N,O-acetal by using 4-toluenesulfonyl acid in an ethanol/methanol mixture gave chromatographically pure diol 3,24 which could be selectively protected at the primary hydroxy group with tert-butyl(dimethyl)silyl chloride to supply 11 in 80% over three steps from 8. Note that this silylation is much more easily achieved than that of the similar Boc-amine diol 2 derived from Garner’s aldehyde, which tends to give disilyl products if great care is not taken.

To confirm our stereochemical assignment of the vinyl addition, the known oxazolidinone 9 was formed in 75% yield from 11 by using triphosgene and pyridine. Unfortunately, the 1H NMR spectrum reported in the literature was not sufficiently resolved to permit comparison of coupling constants, but, in general, the H-4 to H-5 coupling (oxazolidinone numbering) can be easily used to distinguish between the cis- and trans-diastereomers, with cis $J_{4,5} = 7$ Hz and the trans $J_{4,5} = 4$ Hz.20 Oxazolidinone 9 has $J_{4,5}$ of 7.6 Hz, indicative of a cis-relationship. In addition, removal of the toluenesulfonyl protecting group could be accomplished in good yield (83%) by using Na/naphthalene in 1,2-dimethoxyethane, and the cis-coupling constant between H5 at $\delta = 5.04$ ppm and H4 at $\delta = 3.83$ ppm of oxazolidinone 6 was revealed to be 8.1 Hz, matching that reported by Ibuka,18 and thereby confirming our assignment of the anti-diastereomer 10 from the Grignard chemistry. Note that this synthetic route to 6 via N-tosyl serinal 8 is a significant improvement compared with previously reported Grignard chemistry.

In our case, we had no desire to remove the N-tosyl protection; instead, we sought to deprotect the primary hydroxy and to oxidize it to a carboxylic acid to form our β-VSer synthetic equivalent. Although there are reports of both steps being achieved in one pot with KF, Jones reagent, or similar compounds25 we found it better to do this in a stepwise manner by using HCl and MeOH to remove the silyl protection in 92% yield, and subsequent Jones oxidation to supply methyl ester 12 in 82% yield after diazomethane treatment. Unfortunately, attempts at oxidation with TEMPO-type reagents did not give a complete reaction, giving yields of around 50% in our hands.

Although we desired the N-tosyl protection, we recognize its versatility is limited for some cases, so we demonstrated that the final steps can also be carried out with a p-nosyl-protected nitrogen. From 6, the para-nosyl group can be introduced using sodium hydride in THF to give 13 in 90% yield. Similar reactions have been reported to run in DMF and to give concomitant silyl ether cleavage,26 but in our case a mixture was always observed. Therefore, we removed the silyl ether under acidic conditions and employed a Jones oxidation, as described earlier for 12, to give 14 in similar yields.

In summary, an efficient synthesis of a β-vinyl serine (β-VSer) synthetic equivalent is reported that exploits the sterodirecting effect of the N-toluenesulfonylamide group in a highly diastereoselective vinyl Grignard addition.

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### Supporting Information

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References and Notes


(21) N-[[(1R,2S)-2-Hydroxy-1-(hydroxymethyl)but-3-en-1-yl]-4-methylbenzenesulfonylamide (3) A 1.6 M solution of vinylmagnesium chloride in THF (18.9 mmol, 11.8 mL, 4 equiv) was added dropwise over 30 min to a solution of the aldehyde 8 (1.34 g, 4.74 mmol) in THF (44 mL) at −40 °C. The solution was then warmed to 0 °C and stirred overnight at rt. The solution was then poured into cold sat. aq NH4Cl and extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried (Na2SO4), filtered, and concentrated to give crude product 10 as a colorless viscous oil; yield: 1.5 g. 1H NMR (400 MHz, CDCl3): δ = 7.85–7.72 (m, 2 H), 7.39–7.29 (m, 2 H), 5.95–5.76 (m, 1 H), 5.49–5.23 (m, 2 H), 4.47 (dd, J = 5.2, 2.4 Hz, 1 H), 4.01 (dd, J = 9.2, 4.2 Hz, 1 H), 3.91–3.65 (m, 2 H), 2.82 (d, J = 5.4 Hz, 1 H), 2.46 (s, 3 H), 1.72 (s, 3 H), 1.62–1.47 (m, 3 H)
To a solution of the crude vinyl alcohol 10 (~4.74 mmol) in MeOH (80 mL) and EtOH (80 mL) at rt. was added TsOH·H2O (180 mg 0.95 mmol, 2 equiv). The solution was stirred overnight then concentrated to half its original volume, diluted with EtOAc (400 mL), and washed with 2.1 sat. aq NaHCO3–H2O (100 mL). The aqueous phase was back-extracted with EtOAc, and the combined organic extracts were washed with brine (~2×) and dried (Na2SO4). Flash column chromatography (silica gel, 50–75% EtOAc–hexanes) gave an off-white solid; yield: 1.00 g (80%); mp 75–76 °C; Rf = 0.20 (50% EtOAc–hexanes).
1H NMR (400 MHz, CDCl3): δ = 7.81 (d, J = 8.3 Hz, 2 H), 7.34 (d, J = 8.3 Hz, 2 H), 5.82 (ddd, J = 13.7, 10.6, 5.1 Hz, 1 H), 5.44 (d, J = 7.9 Hz, 1 H), 5.37 (bd, J = 17.2, 1 Hz, 1 H), 5.37 (bd, J = 10.6 Hz, 1 H), 4.29 (m, 1 H), 3.86 (dt, J = 11.6, 3.6 Hz, 1 H), 3.51 (dd, J = 11.5, 7.8 Hz, 1 H), 3.28 (dt, J = 7.9, 3.7 Hz, 1 H), 2.54 (d, J = 10.6 Hz, 1 H), 2.46 (s, 3 H), 2.25 (d, J = 7.8, 4.1 Hz, 1 H).
13C NMR (100 MHz, CDCl3): δ = 143.8, 137.4, 136.4, 129.9, 127.1, 117.2, 74.8, 61.8, 57.3, 216. HRMS (ESI-TOF): m/z [M + Na]+ calcd for C12H17NNaO4S: 294.0776; found: 294.0770.


