Published in final edited form as:

Synlett. 2021 ; 32(6): 601–604. doi:10.1055/a-1308-0370.

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

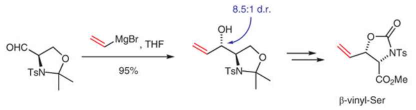
Ernest G. Nolen, **Yuqi M. Cao**, **Brynn D. Lewis**, **Madison H. Powers**, **Andrew W. Thompson**, **John M. Bennett**

Department of Chemistry, Colgate University, 13 Oak Drive, Hamilton, NY 13346, USA

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.

Graphical Abstract



Keywords

vinylserine; alkenyl amino acid; Garner aldehyde; oxazolidinones

As part of our synthetic work directed toward glycopeptide mimetics, we required a suitably protected (2*S*,3*S*)-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.[1] In particular, alkenyl amino acids incorporated into peptides have proven to be useful for peptide stapling by a cross-metathesis reaction to afford conformationally restricted peptidomimetics.[2] In addition, Zhang and van der Donk have examined the effect of direct alkenyl amino acid incorporation.[3] 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 pentenoic backbone of β-VSer itself is also a common scaffold for dipeptide isosteres,[4] which have been investigated as enzyme inhibitors and as receptor antagonists.[5]

---

enolen@colgate.edu .

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1308-0370.

This platform has also been a versatile synthetic intermediate for preparing sphingomyelin analogues[6] and glycosidase inhibitors such as the deoxynojirimycins.[7] It has also served as a building block for antitumor agents such as 2-*epi*-pachastrissamine[8] or for glycopeptide[9] and β-lactam antibiotics.[10] 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[11] and an allylic C–H amination[12] 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-aminopent-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,[13] azide epoxide openings,[6a] and chiral glycine enolate aldols[14] 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 aldehyde[15] or the OTBS-Boc-serinal **4**,[7a,10] followed by an intramolecular cyclization onto the Boc group to form an oxazolidinone. The Grignard approach has been widely used,[7b,9,16] 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.[7a] The typical *anti*-selectivity for vinyl addition to Garner's aldehyde is reported to range from 3:1[16a] 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)$_3$AlH 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 stereodirecting 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-Ser[20] 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-Ala[22] and TsNH-Phe[23] 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% yield[24] (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 **9b** to lie perpendicular to the plane defined by the aldehyde carbonyl as opposed to the C–CH_2O 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−897XD 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 might 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-toluenesulfonic 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 disilylation products if great care is not taken.

To confirm our stereochemical assignment of the vinyl addition, the known oxazolidinone[29] **9** was formed in 75% yield from **11** by using triphosgene and pyridine. Unfortunately, the ^{1}H 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* $J_{4,5} \approx 7$ Hz and the *trans* $J_{4,5} \approx 4$ Hz.[30] 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 compounds[31] 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 TEM-PO-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,[29] 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 stereodirecting effect of the *N*-toluenesulfonamide group in a highly diastereoselective vinyl Grignard addition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

The authors thank the University of Florida’s Mass Spectrometry Research and Education Center for the HRMS measurements.

Funding Information

This work was supported by the National Institutes of Health (GM123534-01A1) and the National Science Foundation (MRI 1726308).National Science Foundation (MRI 1726308)National Institutes of Health (GM123534-01A1)

References and Notes

(1). Ngo JT; Tirrell DA Acc. Chem. Res 2011, 44, 677. [PubMed: 21815659]

(2). (a)Blackwell HE; Grubbs RH Angew. Chem. Int. Ed 1998, 37, 3281.(b)Schafmeister CE; Po J; Verdine GL J. Am. Chem. Soc 2000, 122, 5891.(c)Aillard B; Robertson NS; Baldwin AR; Robins S; Jamieson AG Org. Biomol. Chem 2014, 12, 8775. [PubMed: 25266495] (d)Yeo DJ; Warriner SL; Wilson AJ Chem. Commun 2013, 49, 9131.

(3). Zhang X; van der Donk WA J. Am. Chem. Soc 2007, 129, 2212. [PubMed: 17266311]

(4). Ibuka T; Habashita H; Otaka A; Fujii N; Oguchi Y; Uyehara T; Yamamoto YJ Org. Chem 1991, 56, 4370.

(5). (a)Oishi S; Narumi T; Ohno H; Otaka A; Fujii N Yuki Gosei Kagaku Kyokaishi 2008, 66, 846. (b)Venkatesan N; Kim BH Curr. Med. Chem 2002, 9, 2243. [PubMed: 12470245]

(6). (a)Hakogi T; Yamamoto T; Fujii S; Ikeda K; Katsumura S Tetrahedron Lett 2006, 47, 2627. (b)Yamamoto T; Hasegawa H; Hakogi T; Katumura S Org. Lett 2006, 8, 5569. [PubMed: 17107074] (c)Wisse P; de Geus MAR; Cross G; van den Nieuwendijk AMCH; van Rooden EJ; van den Berg RJBHN; Aerts JMFG; van der Marel GA; Codée JDC; Overkleeft HS J. Org. Chem 2015, 80, 7258. [PubMed: 26061009]

(7). (a)Knight JG; Tchabanenko K Tetrahedron 2003, 59, 281.(b)Takahata H; Banba Y; Sasatani M; Nemoto H; Kato A; Adachi I Tetrahedron 2004, 60, 8199.

(8). Lee D Synlett 2012, 23, 2840.

(9). Wang B; Liu Y; Jiao R; Feng Y; Li Q; Chen C; Liu L; He G; Chen GJ Am. Chem. Soc 2016, 138, 3926.

(10). Murphy-Benenato KE; Dangel B; Davis HE; Durand-Réville TF; Ferguson AD; Gao N; Jahic H; Mueller JP; Manyak EL; Quiroga O; Rooney M; Sha L; Sylvester M; Wu F Zambrowski M, Zhao SX. 2015, 6, 537.

(11). (a)Robertson J; Abdulmalek E Tetrahedron Lett 2009, 50, 3516.(b)Kim H; Yoo D; Choi SY; Chung YK; Kim YG Tetrahedron: Asymmetry 2008, 19, 1965.(c)Martín R; Moyano A; Pericàs MA; Riera A Org. Lett 2000, 2, 93. [PubMed: 10814254] (d)Amador M; Ariza X; Garcia J; Sevilla S Org. Lett 2002, 4, 4511. [PubMed: 12465925]

(12). Fraunhoffer KJ; White MC J. Am. Chem. Soc 2007, 129, 7274. [PubMed: 17516648]

(13). Lee JH; Kang JE; Yang MS; Kang KY; Park KH Tetrahedron 2001, 57, 10071.

(14). (a)Kazmaier U; Pähler S; Endermann R; Häbich D; Kroll H-P; Riedl B Bioorg. Med. Chem 2002, 10, 3905. [PubMed: 12413842] (b)Dubreuil D; Pipelier M; Micouin L; Lecourt T; Lacone V; Bonneville M; Lependu J; Turcot-Dubois A-L WO 2008/047249, 2008.

(15). (a)Garner P; Park JM J. Org. Chem 1988, 53, 2979.(b)Garner P Tetrahedron Lett 1984, 25, 5855.

(16). (a)Passiniemi M; Koskinen AMP Beilstein J. Org. Chem 2013, 9, 2641. [PubMed: 24367429] (b)Coleman RS; Carpenter AJ Tetrahedron Lett 1992, 33, 1697.(c)Ojima I; Vidal ES J. Org. Chem 1998, 63, 7999.(d)Kumar G; Kaur S; Singh V Helv. Chim. Acta 2011, 94, 650.(e)Ghosal P; Shaw AK Tetrahedron Lett 2010, 51, 4140.(f)Bhabak KP; Proksch D; Redmer S; Arenz C Bioorg. Med. Chem 2012, 20, 6154. [PubMed: 22989909]

(17). Herold J Helv. Chim. Acta 1988, 71, 354.

(18). Ibuka T; Mimura N; Aoyama H; Akaji M; Hono H; Miwa Y; Taga T; Nakai K; Tamamura H; Fujii N; Yamamoto YJ Org. Chem 1997, 62, 999.

(19). (a)Myeong I-S; Kim JS; Park M-G; Jeon H-H; Jung C; Lee Y-T; Ham W-H Synthesis 2018, 50, 2058.(b)Yamamoto T; Hasegawa H; Hakogi T; Katsumura S Org. Lett 2006, 8, 5569. [PubMed: 17107074] (c)Jin T; Mu Y; Kim J-S; Park S-H; Jin X; Kang J-C; Oh C-Y; Ham W-H Synth. Commun 2014, 44, 2401.

(20). (a)Jurczak J; Golebiowski A Chem. Rev 1989, 89, 149.(b)Knight JG; Ainge SW; Harm AM; Harwood SJ; Maughan HI; Armour DR; Hollinshead DM; Jaxa-Chamiec AA J. Am. Chem. Soc 2000, 122, 2944.

(21). (a)Çelebi-Ölçüm N; Lam Y.-h.; Richmond E; Ling; Smith AD; Houk KN Angew. Chem. Int. Ed 2011, 50, 11478.(b)Richmond E; Ling KB; Duguet N; Manton LB; Çelebi-Ölçüm N; Lam Y-H;

Alsancak S; Slawin AMZ; Houk KN; Smith AD Org. Biomol. Chem 2015, 13, 1807. [PubMed: 25501712]

(22). Gryko D; Urbańczyk-Lipkowska Z; Jurczak J Tetrahedron: Asymmetry 1997, 8, 4059.

(23). Reginato G; Pezzati B; Ienco A; Manca G; Rossin A; Mordini AJ Org. Chem 2011, 76, 7415.

(24). N-[(1*R*,2*S*)-2-Hydroxy-1-(hydroxymethyl)but-3-en-1-yl]-4-methylbenzenesulfonamide (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 NH_4Cl and extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated to give crude product **10** as a colorless viscous oil; yield: ~1.5 g. ^{1}H NMR (400 MHz, $CDCl_3$): 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 (td, *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)**8**$_{424}$**10**$^{1}{}_{3}$ To a solution of the crude vinyl alcohol **10** (~4.74 mmol) in MeOH (80 mL) and EtOH (80 mL) at r.t. was added TsOH·H_2O (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 $NaHCO_3$–H_2O (100 mL). The aqueous phase was back-extracted with EtOAc, and the combined organic extracts were washed with brine (×2) and dried (Na_2SO_4). Flash column chromatography (silica gel, 50–75% EtOAc–hexanes) gave an off-white solid; yield: 1.00 g (80%); mp 75–76 °C; R_f = 0.20 (50% EtOAc–hexanes).**10**$_{23224}$ ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 8.3 Hz, 2 H), 7.34 (d, *J* = 8.3 Hz, 2 H), 5.82 (ddd, *J* = 17.3, 10.6, 5.1 Hz, 1 H), 5.44 (d, *J* = 7.9 Hz, 1 H), 5.37 (bd, *J* = 17.2, 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 (ddd, *J* = 11.5, 7.8, 3.8 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 (dd, *J* = 7.8, 4.1 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl^3$): δ = 143.8, 137.4, 136.4, 129.9, 127.1, 117.2, 74.8, 61.8, 57.3, 21.6. HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{12}H_{17}NNaO_4S$: 294.0776; found: 294.0770.$^{1}{}_{3}{}^{133+}{}_{12174}$

(25). (a)Ageno G; Banfi L; Cascio G; Guanti G; Manghisi E; Riva R; Rocca V Tetrahedron 1995, 51, 8121.(b)Williams L; Zhang Z; Shao F; Carroll PJ; Joullié MM Tetrahedron 1996, 52, 11673.

(26). Mengel A; Reiser O Chem. Rev 1999, 99, 1191. [PubMed: 11749444]

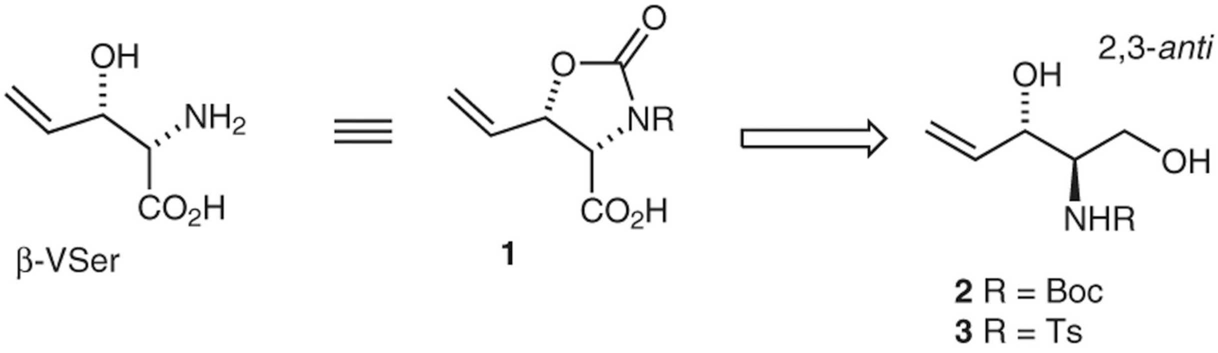
(27). (a)Malins LR; Payne RJ Org. Lett 2012, 14, 3142. [PubMed: 22642500] (b)Giltrap AM; Haeckl FPJ; Kurita KL; Linington RG; Payne RJ J. Org. Chem 2018, 83, 7250. [PubMed: 29798664]

(28). Bayquen AV; Read RW Tetrahedron 1996, 52, 13467.

(29). Knight JG; Lawson IM; Johnson CN Synthesis 2006, 227.

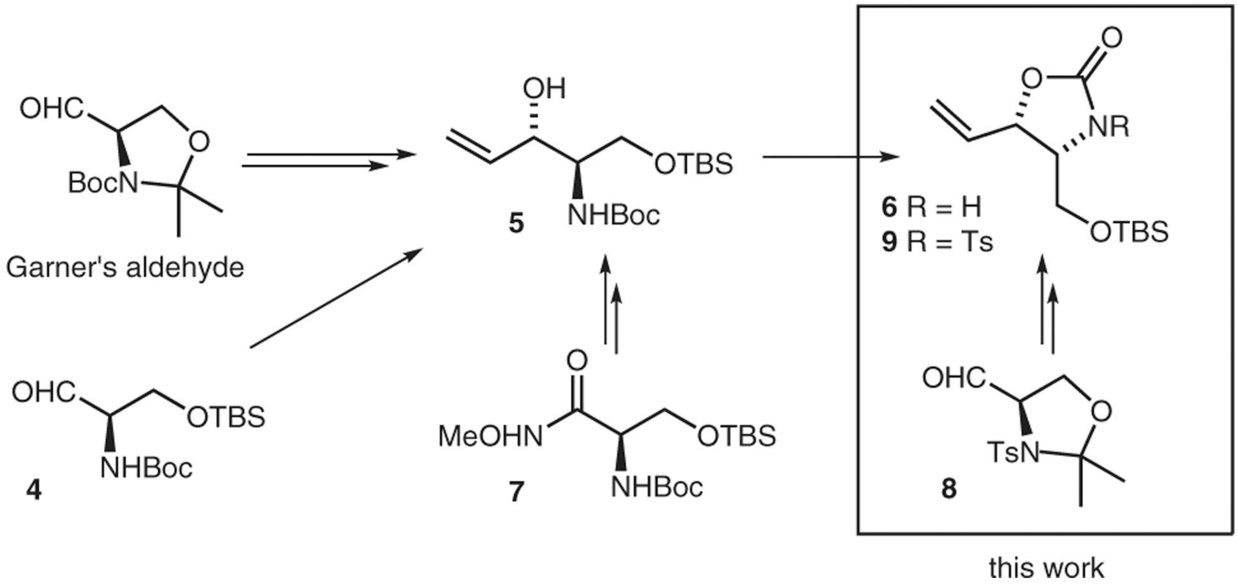
(30). (a)Myeong I-S; Lee Y-T; Lee S-H; Jung C; Kim J-S; Park S-H; Kang J; Lee S-J; Ye I-H; Ham W-H Tetrahedron: Asymmetry 2017, 28, 1053.(b)Zamani F; Pyne SG; Hyland CJT Org. Chem 2017, 82, 6819.

(31). (a)Liu H-J; Han I-S Synth. Commun 1985, 15, 759.(b)Laib T; Chastanet J; Zhu JJ Org. Chem 1998, 63, 1709.

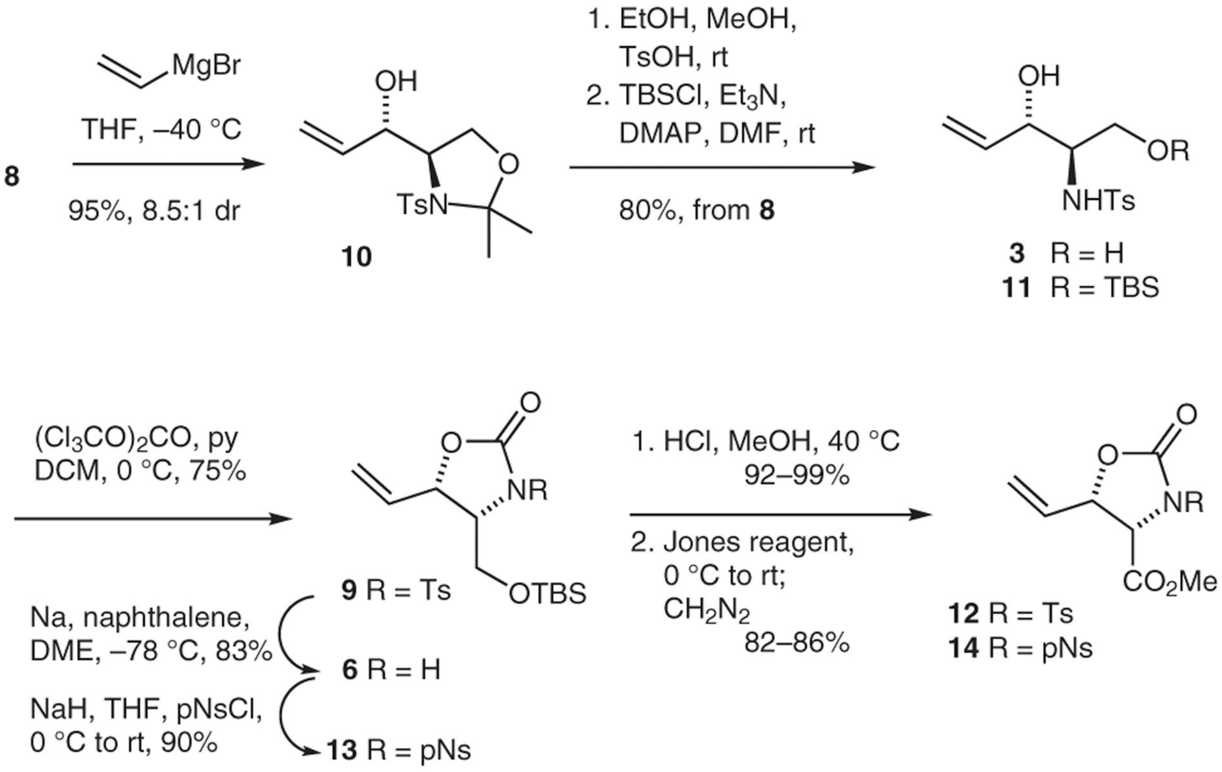


Scheme 1.

Target β-vinylserine (β-VSer) synthetic equivalent **1** and precursor

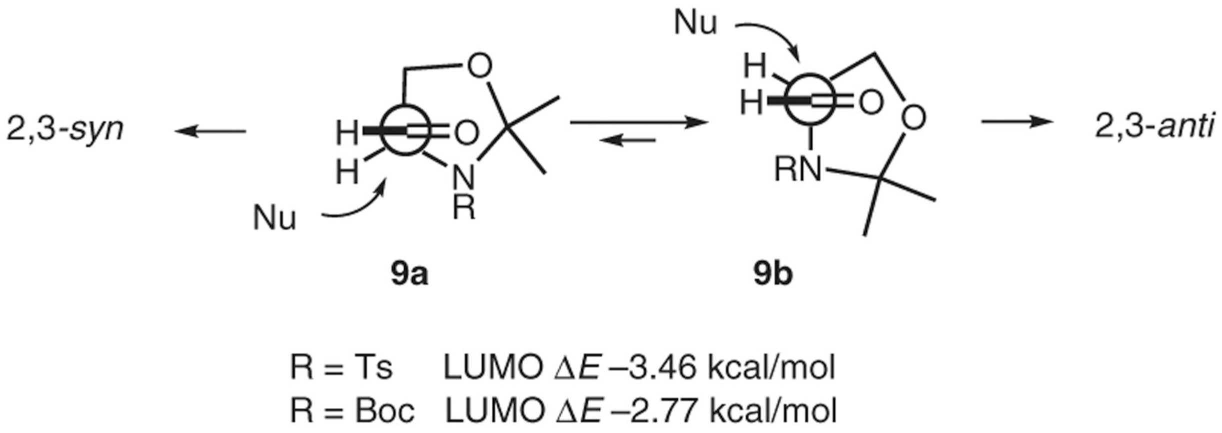


Scheme 2.
Approaches to *cis*-oxazolidinones



Scheme 3.

Synthesis of β-VSer derivatives **12** and **14**; pNs = 4-$O_2NC_6H_4SO_2$.

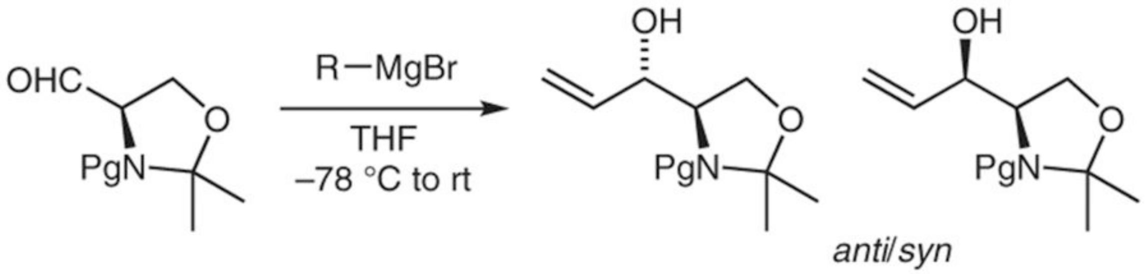


Scheme 4.

Felkin–Anh depiction of nucleophilic attacks

Table 1

Comparison of Grignard Additions to **8** and to Garner's Aldehyde



Entry	R	Pg = Ts *anti/syn*[a]	Yield[b] (%)	Pg = Boc *anti/syn*	Ref.
1	vinyl	8.5:1	95	3–6:1	7b,9,16
2	Ph	12:1	70	1.5–5:1	27,25b
3	4-MeOC$_6$H$_4$	14:1	n.d.[c]	5:1[d]	27
4	Me	7:1	93	2:1	25a
5	Et	8:1	87[e]	1:9	25a
6	All	1:1.6	94	1.5:1	28

[a] Determined by ^{1}H NMR integration on the crude sample or after hydrolysis to the diol.

[b] The crude product contained 1–4% of starting aldehyde.

[c] Not determined due to contamination by anisole. Hydrolysis gave the diol in 59% yield over two steps.

[d] Aryllithium rather than Grignard.

[e] *anti*-Configuration confirmed by comparison with hydrogenated **10**.