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Stereodivergent Approach to β-Hydroxy α-Amino Acids from C_2-Symmetrical Alk-2-yne-1,4-diols

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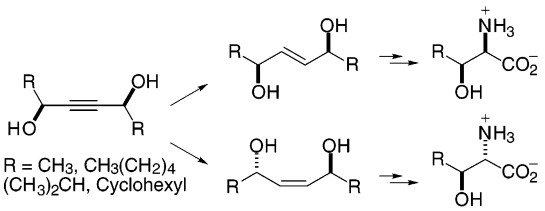
ABSTRACT



A new stereodivergent route to *erythro*- and *threo*-β-substituted serines from a common C_2-symmetrical alk-2-yne-1,4-diol is described. Stereocontrol in such an acyclic system is achieved by taking advantage of symmetry. Stereoselective alkyne reduction to either (*Z*)- or (*E*)-olefin allows selection of the stereochemistry of α-carbon in the final amino acid by using a Pd(0)-catalyzed process. This strategy has been applied to the synthesis of (2*S*,3*S*)-3-hydroxyleucine.

β-Hydroxy α-amino acids are structural components of many complex natural products with interesting pharmacological properties.[1] For example, some of them are found in peptides possessing antibiotic or immunosuppressant activities.[2] Furthermore, these functionalized amino acids have also been used as intermediates in asymmetric synthesis of numerous compounds,[3] including β-lactames.[4] As a result of their major significance in biological systems, a number of elegant stereoselective approaches have been described for their preparation.[5] These strategies include some catalytic processes (viz. Sharpless AD and AE,[6] aldol reactions,[7] catalytic hydrogenations,[8] or enzymatic methods[9]).

Although most of these catalytic methods afford *threo*-β-hydroxy α-amino acids in good yields and selectivity, reliable procedures that lead to either *erythro* or *threo* isomers proved to be elusive.[10] Herein, we report an efficient method for a selective preparation of both diastereoisomers from a common precursor, a C_2-symmetrical alk-2-yne-1,4-diol (**1**). As we have recently reported, such diols can be readily available by stereoselective reduction of the parent acetylenic diketones[11] or by stereoselective addition of alk-1-yn-3-ols to aldehydes.[12]

The key features of our synthesis (Scheme 1) are (i) a selective transformation to the corresponding (*E*)- or (*Z*)-allylic dicarbamates (**4** or **5**); (ii) desymmetrization and stereoselective conversion to either *trans*- or *cis*-oxazolidinones (**6** and **7**, respectively) by a Pd(0)-catalyzed allylic alkylation; and (iii) oxidative cleavage of the double bond and final deprotection to afford the selected β-substituted serines. As far as the stereoselectivity is concerned, the configuration of the starting diols would determine the β-carbon configuration of the final product. On the other

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(4) (a) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49−56. (b) Labia, R.; Morin, C. *J. Antibiot.* **1984**, *37*, 1103−1129. (c) Floyd, D. M.; Fritz, A. W.; Pluscec, J.; Weaver, E. R.; Cimarusti, C. M. *J. Org. Chem.* **1982**, *47*, 5160−5167.

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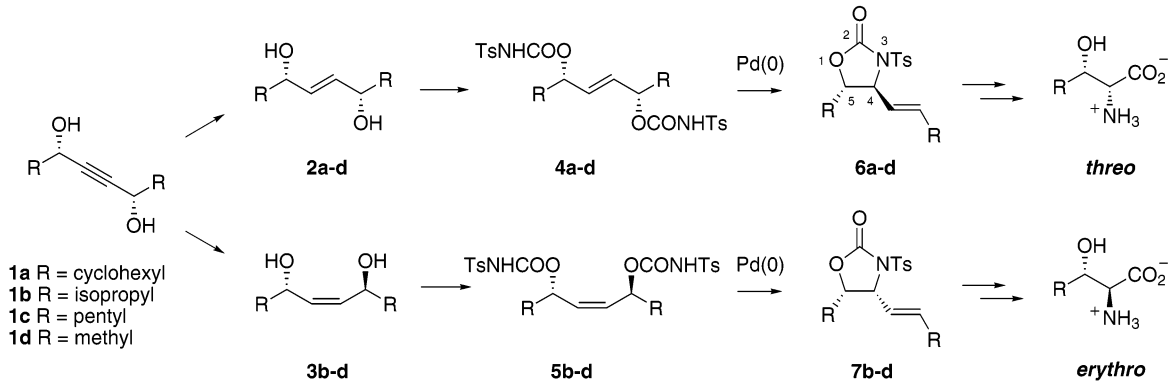
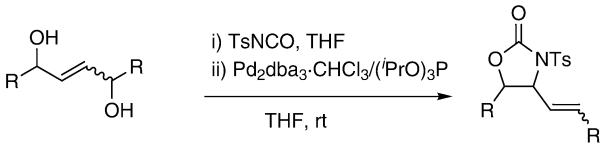
Scheme 1



hand, we expected that the configuration of the α-carbon could be selected by an appropriate stereoselective alkyne reduction.[13] Thus, (*E*)-unsaturated diols (**4**) would afford *trans*-oxazolidinones (**6**), whereas (*Z*)-olefins (**5**) would give access to *cis*-oxazolidinones (**7**), which are direct precursors of the *β*-substituted serines.

Our first efforts were directed to the cyclization of (*E*)-allylic alcohols. Thus, diol **2a** was treated with 2.5 equivalents of tosyl isocyanate in THF at room temperature to afford the transient dicarbamate **4a**, which was converted in situ to the oxazolidine **6a** in a Pd(0)-catalyzed process (Pd_2dba_3·$CHCl_3$/(^{i}PrO)$_3$P).[14] As expected, only the (*E*)-*trans*-oxazolidine **6a** isomer was detected.[15] The same behavior was observed for other diols, which also afforded a single diastereoisomer (**6**)[16] (Table 1, entries 1−3).

Table 1. Pd(0)-Catalyzed Cyclization of Diols **2** and **3**[a]

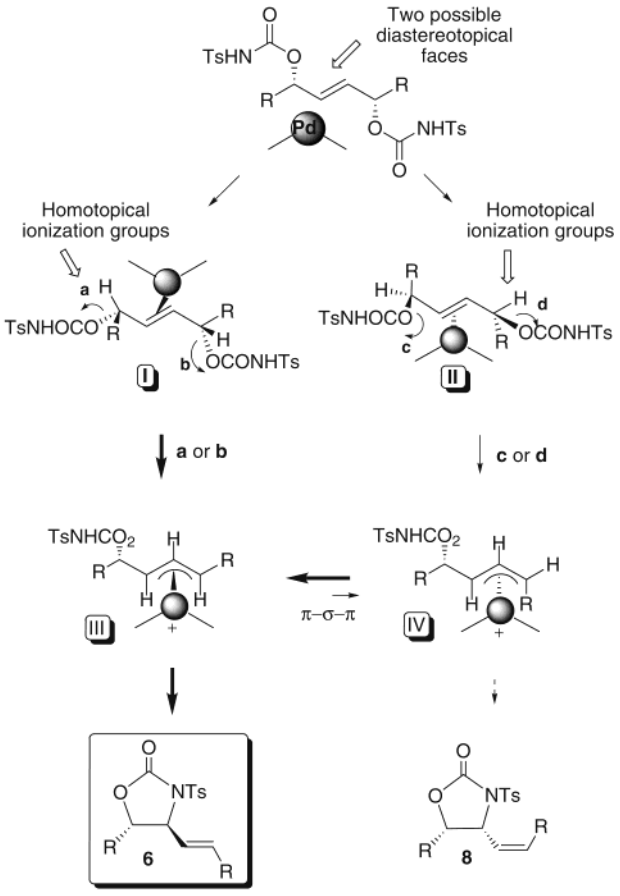


entry	diol	R	yield[b]	product	dr (%)[c]
1	**2a**	cyclohexyl	70%	**6a**	>95:5
2	**2b**	isopropyl	85%	**6b**	>95:5
3	**2c**	pentyl	75%	**6c**	>95:5
4	**2d**	methyl	93%	**6d**	58:42
5[d,e]	**3b**	isopropyl	70%	**7b**	>95.5
6[e,f]	**3c**	pentyl	75%	**7c**	>95:5
7[d]	**3d**	methyl	89%	**7d**	90:10

[a] Typical conditions: 2.5 equiv of TsNCO, 4 mol % Pd_2dba_3·$CHCl_3$, 24 mol % P(O^{i}Pr)$_3$. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Dicarbamates **5b** and **5d** were first isolated and then cyclized in CH_3CN.[17] [e] Catalyst load: 6−12 mol % Pd_2dba_3·$CHCl_3$ and 36−72 mol % P(O^{i}Pr)$_3$. [f] Performed in 1:1 THF/CH_3CN.

The origin of such a remarkable acyclic stereoselection is based on the symmetry properties of the substrate (Scheme 2). Pd can be complexed unequally to both diastereotopical faces of the olefin (complexes **I** or **II**), but when these complexes ionize, each one can form initially[18] a single *π*-allyl complex (**III** and **IV**, respectively). Then, the intramolecular cyclization would afford preferentially two diastereoisomers: the observed (*E*)-*trans*-oxazolidinone **6** and the isomeric (*Z*)-*cis*-oxazolidinone **8**. In general, the (*E*)-trans isomer seems to be favored by sterical interactions not only on the *π*-allyl complexes but also on the ionization or cyclization transition state. However, when R is a smaller group (i.e., methyl), such interactions are less important, and in fact, a mixture of **6d** and **8d** is obtained (Table 1, entry 4).

Scheme 2



A similar analysis for (*Z*)-allylic dicarbamates **5** (Scheme 3) can be performed. In contrast to the (*E*)-isomer, in this case only a single olefin complex (**V**) is possible since both alkene faces are homotopical. The ionization process could lead to two possible π-allyl intermediates (**VI** or **VII**) where again one could be favored over the other by sterical constraints. Interestingly, the expected preferred isomer would be the (*E*)-*cis*-oxazolidinone **7**. According to this prediction, when dicarbamate **5b** was submitted to our conditions, only the desired isomer (**7b**) was obtained (entry 5).[19] Similarly, dicarbamate **5c** afforded stereoselectively the expected (*E*)-*cis*-oxazolidinone (**7c**). Only when the sterically less hindered dicarbamate **5d** was used, was the minor isomer **9d** detected in a 90:10 ratio.

The methodology can also be applied to *meso*-diols **10** and **11** (Table 2) in good yields and with high diastereoselectivities. In the case of diols **10** (entries 1−3), both faces are enantiotopical and the diastereoselection occurs after the complexation step. As a result, oxazolidinones **7** were obtained as the major diastereoisomers. Obviously, as achiral palladium ligands are used, a racemic product is obtained. Alternatively, diols **11** afforded (*E*)-*trans*-oxazolidinones **6** (entries 4−6) through a mechanism where we assumed that the complexation is now the diastereoselective process, whereas ionization is an enantioselective one.

Transformation of oxazolidinones **6** and **7** into acids **12** and **13**, respectively, was successfully accomplished by ozonolysis followed by oxidation of the crude aldehyde with $NaClO_2$[20] without loss of stereochemical purity (Scheme 4). This two-step process gave better yields than direct olefin cleavage with $RuCl_3$.[21]

Scheme 3

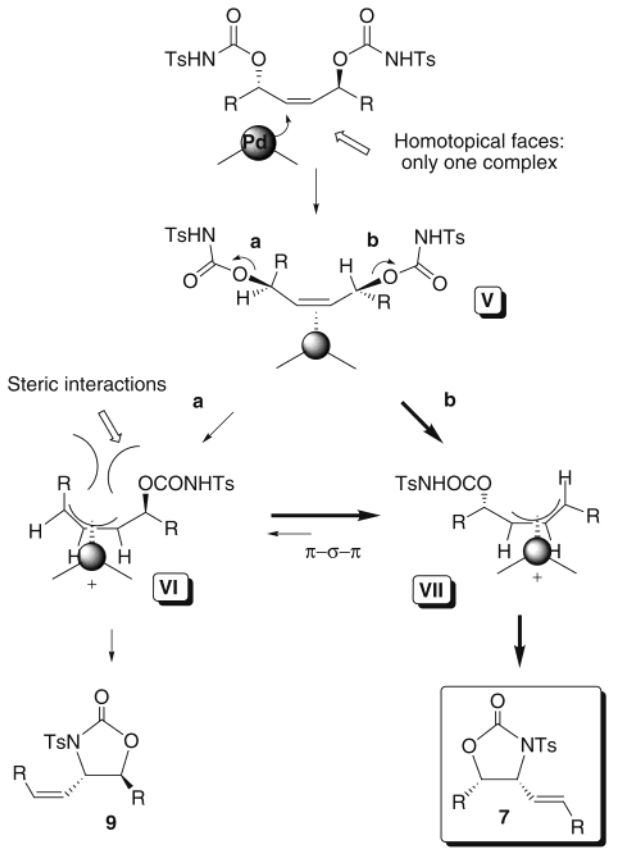
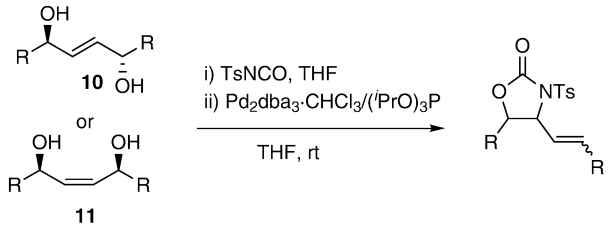


Table 2. Pd(0)-Catalyzed Cyclization of *meso*-Diols[a]



entry	diol	R	yield	product	dr (%)[b]
1[c]	**10a**	cyclohexyl	82%	**7a**	>95:5
2[c]	**10c**	pentyl	68%	**7c**	>95:5
3[c]	**10d**	methyl	86%	**7d**	90:10[d]
4	**11a**	cyclohexyl	96%	**6a**	>95.5
5	**11c**	pentyl	69%	**6c**	>95:5
6	**11d**	methyl	84%	**6d**	93:7[e]

[a] Typical conditions: 2.5 equiv of TsNCO, 4 mol % $Pd_2dba_3{\cdot}CHCl_3$, 24 mol % $P(O^iPr)_3$. [b] Determined by ^1H NMR analysis. [c] Dicarbamate was first isolated and then cyclized in CH_3CN. [d] Minor isomer **9d**. [e] Minor isomer **8d**.

(6) See, for example: (a) Shao, H.; Goodman, M. *J. Org. Chem.* **1996**, *61*, 2582−2583. (b) Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.* **1989**, *30*, 6637−6640. (c) Schmidt, U.; Respondek, M.; Lieberknecht, A.; Werner, J.; Fischer, P. *Synthesis* **1989**, 256−261.

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(10) Some remarkable exceptions are: (a) Evans, D. A.; Janey, J. M.; Magomedov, N.; Tedrow, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1884−1888. (b) Kuwano, R.; Okuda, S.; Ito, Y. *J. Org. Chem.* **1998**, *63*, 3499−3503. (c) Sunazuka, T.; Nagamitsu, T.; Tanaka H.; Omura, S.; Sprengeler, P. A.; Smith A. B. III. *Tetrahedron Lett.* **1993**, *34*, 4447−4448.

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(12) Amador, M.; Ariza, X.; Garcia, J.; Ortiz, J. *Tetrahedron Lett.* **2002**, *43*, 2691−2694.

(13) Allylic diols **2** and **3** were easily obtained from acetylenic diols **1** by $LiAlH_4$ reduction and partial hydrogenation (H_2, Lindlar catalyst, EtOAc), respectively.

(14) For related cyclizations, see: (a) Hayashi, T.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1987**, *28*, 4837−4840. (b) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 1261−1263.

(15) The stereochemistry was assigned by NOE experiments and spectral data comparison with similar oxazolidinones: Kimura, M.; Tanaka, S.; Tamaru, Y. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1689−1705.

(16) HPLC analysis of **6b** derived from **2b** (>99% ee) showed a single stereoisomer on a chiral column (Chiralcel OD-H, 9:1 hexane/2-propanol, 0.5 mL/min, $t(-) = 12.7$ min, $t(+) = 16.3$ min).

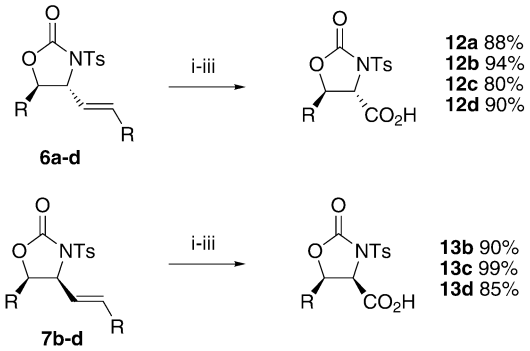
(17) Acetonitrile improved the reaction rates and stereoselectivity.

(18) Both π-allyl complexes are amenable to $\pi-\sigma-\pi$ isomerization.

(19) HPLC analysis of **7b** on a Chiralcel OD-H column showed a single enantiomer (9:1 hexane/2-propanol, 0.5 mL/min, $t(+) = 16.6$ min, $t(-) = 21.1$ min).

(20) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567−569.

Scheme 4[a]



[a] Reaction conditions: (i) O_3/CH_2Cl_2; (ii) Me_2S; (iii) $NaClO_2$, H_2O_2, NaH_2PO_4, CH_3CN-H_2O.

Finally, compound **13b** was detosylated under reductive conditions (Na/naphthalene)[22] to afford a known compound **14b** that can be hydrolyzed to the free β-hydroxyleucine[23] (Scheme 5).

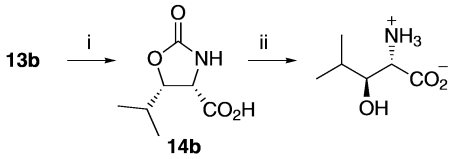
In summary, we have developed a new catalytic, stereodivergent approach to both *erythro*- and *threo*-protected

(21) Carlsen, H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

(22) Removal of tosyl group was successfully carried out in a number of oxazolidinones **12** or **13** in 65−94%: Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A. J.; Bank, S.; Closson, W. D.; Wriede, P. A. *J. Am. Chem. Soc.* **1967**, *89*, 5311−5312.

(23) Spectral data fully agree with those reported: (a) Hale, K. J.; Manaviazar, S.; Delliser, V. M. *Tetrahedron* **1994**, *50*, 9181−9188. (b) Laïb, T.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1998**, *63*, 1709−1713.

Scheme 5[a]



[a] Reaction conditions: (i) Na/Naphthalene (5 equiv); (ii) ref 23b.

β-hydroxy α-amino acids series that takes advantage of the C_2-symmetrical properties of our starting material. Furthermore, we have demonstrated that cyclization of dicarbamates derived from acyclic alk-2-ene-1,4-diols can be stereoselective. In this sense, it has been possible to force the cyclization toward the more sterically congested *cis*-4,5-disubstituted oxazolidinones.

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Supporting Information Available: Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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