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Selective Access to *E*- and *Z*-ΔIle-Containing Peptides via a Stereospecific E2 Dehydration and an O → N Acyl Transfer

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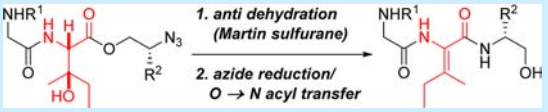
Supporting Information

ABSTRACT: A concise synthesis of peptides that contain *E*- or *Z*-dehydroisoleucine (ΔIle) residues is reported. The key reaction is an unusual *anti* dehydration of *β-tert*-hydroxy amino acid derivatives that is mediated by the Martin sulfurane. A subsequent tandem Staudinger reduction−O → N acyl transfer process forges an amide bond to the ΔIle residue with minimal *E*/*Z* alkene isomerization. Density functional calculations attribute the stereospecific dehydration to a highly asynchronous E2 *anti* process.



α,β-Dehydroisoleucine (ΔIle) is present in several bioactive natural products including phomopsin A and yaku'amide A (Figure 1).[1] *E*-ΔIle is more common than its *Z*-isomer, with

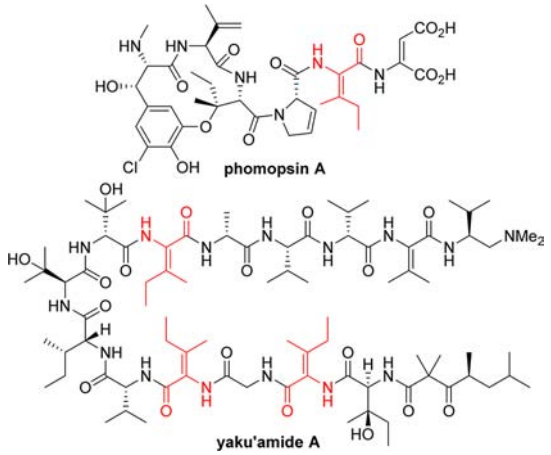
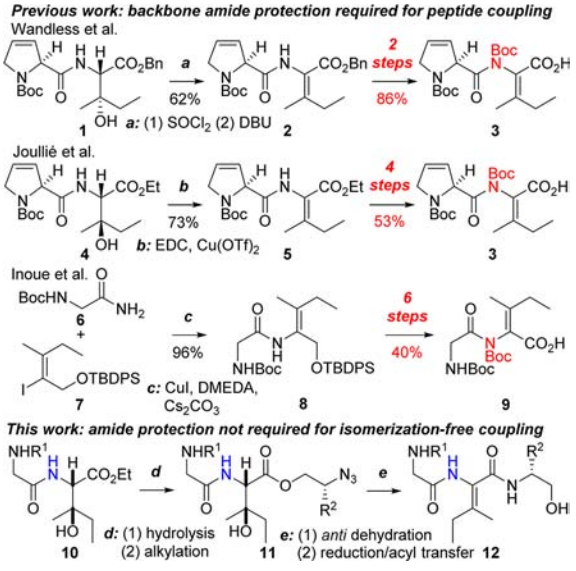


Figure 1. Representative natural products that contain ΔIle.

yaku'amides A and B[1a] representing the only natural products isolated to date that contain the latter residue. Bulky dehydroamino acids such as ΔIle are valued for their rigidifying effect on peptides[2,3] and their increased stability to proteases relative to standard amino acids.[4] Accordingly, new and efficient methods that facilitate their stereoselective incorporation into peptides are in demand.

As part of synthetic efforts targeting the phomopsins, the Wandless[5] and Joullié[6] groups developed stereospecific dehydrations of *β*-hydroxyisoleucine (*β*-OHIle) derivatives for constructing *E*-ΔIle (Scheme 1). In the course of preparing yaku'amide A, Inoue et al. devised a different strategy for accessing *E*- and *Z*-ΔIle featuring a Cu-catalyzed coupling reaction.[7] Unfortunately, in each case peptide coupling of the *C*-terminal ΔIle requires protection of the neighboring amide in

Scheme 1. Syntheses of ΔIle-Containing Peptides



order to prevent generation of an azlactone that readily undergoes alkene isomerization.[6,7] Herein, we report the incorporation of *E*- and *Z*-ΔIle into peptides without recourse to amide protection. Our strategy features an O → N acyl transfer reaction[8] and relies on an unusual *anti* dehydration of tertiary alcohols that is mediated by the Martin sulfurane.[9,10]

Recently, we found that OsO_4-catalyzed base-free aminohydroxylations[11] can be conducted on trisubstituted alkenes with complete regioselectivity, affording rapid access to derivatives of *β-tert*-hydroxy amino acids.[12] In the context of this study, we generated a ΔVal-containing peptide via dehydration of *β*-OHVal. In an effort to extend this aminohydroxylation−

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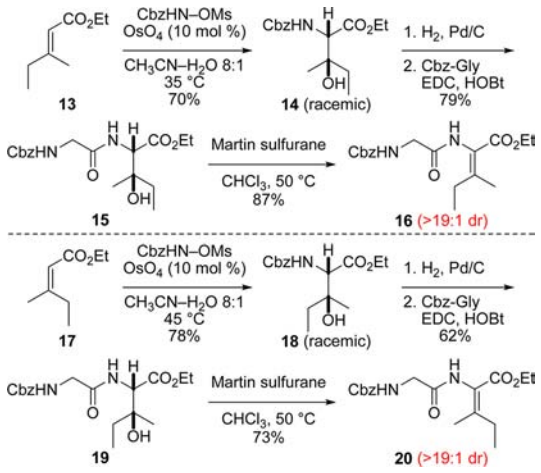
dehydration strategy to the construction of ΔIle derivatives, we examined the aminohydroxylation of *E*-enoate **13** (Scheme 2).

Scheme 2. Synthesis and *anti* Dehydration of 15 and 19



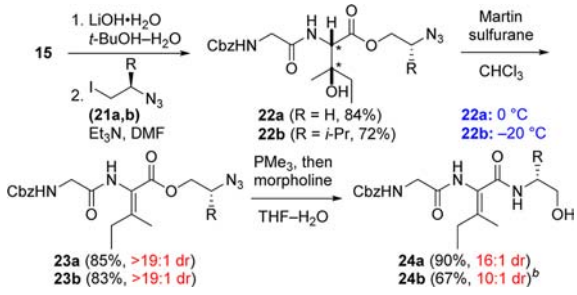
This alkene reacted sluggishly when CbzHN−OC(O)*p*-ClPh[11] was employed as the nitrogen source reagent, and copious quantities of benzyl carbamate ($CbzNH_2$) were obtained. Inspired by the work of Donohoe et al. on tethered aminohydroxylations,[13] we reasoned that a less basic leaving group on the carbamate would improve the reaction. Indeed, CbzHN−OMs gave significantly better results, as racemic *β*-OHIle derivative **14** was produced in good yield (70%) along with smaller amounts of $CbzNH_2$ byproduct. While this work was in progress, the virtues of sulfonyloxycarbamates as reagents for base-free aminohydroxylations were noted by McLeod et al.[14]

Hydrogenolysis of **14** and coupling of the resulting free amine to Cbz-Gly afforded dipeptide **15**. Since dehydrations of tertiary alcohols with the Martin sulfurane are reported to proceed via E1-like mechanisms,[9,15] we were not expecting this reagent to dehydrate **15** stereoselectively. We were therefore surprised to find that exposure of **15** to the Martin sulfurane furnished *Z*-ΔIle-containing dipeptide **16** as the product of clean *anti* dehydration. No minor isomers were visible by ^{1}H NMR. While *anti*-selective or E2-like dehydrations of tertiary alcohols promoted by this reagent are not unprecedented,[16] they are much less common than E1-like dehydrations of these substrates. In our hands, application of the Wandless protocol to **15** delivered **16** with varying levels of selectivity (4−8:1 dr), so we continued our studies with the Martin sulfurane as our reagent of choice.[17] Importantly, we were able to establish the stereospecific nature of this process by applying the four-step sequence developed with *E*-enoate **13** to *Z*-enoate **17** (Scheme 2). The dehydration of dipeptide **19** produced *E*-ΔIle-containing peptide **20** as a single detectable isomer.

Since standard peptide couplings would scramble the alkene stereochemistry in the absence of amide protection, we considered other strategies (e.g., Staudinger ligations,[18] thioacid−based couplings,[19] and $B(OCH_2CF_3)_3$[20]) for elaborating **16**. In preparation for evaluating these methods, we hydrolyzed the ethyl ester of **16**. Surprisingly, saponification was sluggish and accompanied by alkene isomerization (ca. 2:1 dr). Presumably, the hindered nature of the ester moiety allows enolization via *γ*-deprotonation to compete with saponification, thereby enabling isomerization. In contrast, Shangguan and Joullié reported the isomerization-free saponification of a related ΔIle-derived ester,[6] demonstrating the impact of subtle structural differences on the reactivity of these compounds. We next attempted to perform the aminohydroxylation on a substrate possessing an activated carboxylate group that could be employed directly in a subsequent amidation. Although the phenyl ester[21] analogous to **17** was a viable aminohydroxylation substrate, problems with the deprotection and coupling steps caused us to abandon this approach.

Attempted dehydrations of tripeptides with a *β*-hydroxy amino acid as the central residue did not proceed, demonstrating the necessity of performing the dehydration prior to amidation. At this stage, we were drawn to O → N acyl transfer chemistry[8] as a means of precluding alkene isomerization without resorting to protection of the neighboring backbone amide. We envisioned that *β*-azidoethyl esters could be stereoselectively dehydrated and then converted into amides via a tandem reduction/rearrangement process. The requisite substrates were constructed via saponification of ester **15** followed by alkylation with iodides **21a** and **21b** (Scheme 3).[22] Alkylative esterification was

Scheme 3. Stereoselective Synthesis of *Z*-ΔIle-Containing Peptides 24a and 24b[a]



[a]Asterisks on adjacent atoms indicate the portrayal of relative stereochemistry. [b] The conversion of **23b** into **24b** was conducted with piperidine instead of morpholine as the base.

necessary to avoid nonselective dehydration that would occur under typical conditions (i.e., DCC), and iodides **21a** and **21b** were selected to serve as surrogates for the simplest (Gly) and bulkiest (Val) amino acids that are coupled to the *C*-termini of ΔIle residues in yaku'amide A. Esters **22a** and **22b** were produced in good yields, with the latter generated as an inconsequential mixture of diastereomers due to the racemic nature of **15**.

Pleasingly, the esters underwent stereoconvergent *anti* dehydration when exposed to the Martin sulfurane, furnishing *Z*-ΔIle derivatives **23a** and **23b** as single isomers. Dehydration of **22a** was clean at 0 °C, whereas a small amount of *E*-isomer was obtained when the bulkier **22b** was dehydrated at 0 °C (ca. 7:1 dr). Fortunately, only the desired *Z*-**23b** was observed when the reaction was maintained at −20 °C. Staudinger reduction of azides **23a** and **23b** was facile, and addition of an amine base to the mixture upon completion of the reduction triggered O → N acyl transfer, producing amides **24a** and **24b** in good yields. Minor amounts of alkene isomerization occurred during this process (≥10:1 dr), but to our knowledge these are the best results to date for amidations of ΔIle derivatives in the absence of backbone amide protecting groups. This *anti* dehydration−O → N acyl transfer strategy worked equally well for the production of *E*-ΔIle-containing peptides (Scheme 4). Dehydrations of esters **25a** and **25b** were conducted at the same temperatures as the corresponding reactions in the *Z*-series, and isomerically pure

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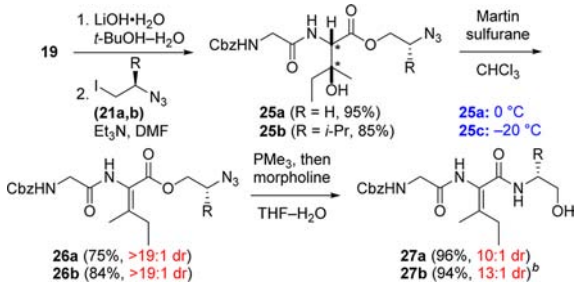
Scheme 4. Stereoselective Synthesis of *E*-ΔIle-Containing Peptides 27a and 27b[a]

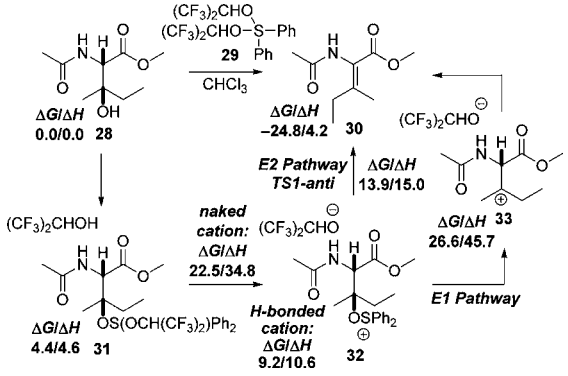


[a]Asterisks on adjacent atoms indicate the portrayal of relative stereochemistry. [b] The conversion of **26b** into **27b** was conducted in DMF−H_2O instead of THF−H_2O.

alkenes were obtained. The reduction and rearrangement of esters **26a** and **26b** proceeded without incident, delivering the targeted amides in excellent yields with minimal *E*-to-*Z* isomerization (≥10:1 dr).

The high stereoselectivity facilitated by the Martin sulfurane was unexpected since earlier reports have proposed that tertiary alcohols may undergo elimination via an E1-like mechanism.[9,15] However, at least one study suggests the feasibility of an E2-type dehydration.[16] This prompted us to employ density functional calculations (Gaussian 09)[23] to examine E1, E2, and $E1_{cb}$ pathways for our *anti* dehydration using alcohol **28** (Scheme 5,

Scheme 5. M06-2X/6-31+G(d,p) [$CHCl_3$, SMD Solvent] Energies for Dehydration (kcal/mol)



a model of substrate **15**) and sulfurane **29** (a slightly simplified version of the Martin sulfurane). M06-2X/6-31+G(d,p) theory[24] was selected since it provides accurate E2 transition state barriers.[25] Geometry optimizations and normal-mode frequency analysis were carried out in $CHCl_3$ using the SMD implicit solvent model.[26]

The reaction of **28** with sulfurane **29** creates an equivalent of $(CF_3)_2CHOH$ and intermediate **31**, which is endergonic by 4.4 kcal/mol. Subsequent loss of the alkoxide $(CF_3)_2CHO^-$ generates the $-OSPh_2$ leaving group. Complete dissociation of $(CF_3)_2CHO^-$ requires 22.5 kcal/mol of free energy, so it is possible that this anion does not actually leave the solvation sphere of **31**. Indeed, structure **32** contains a hydrogen bond between the alkoxide and the amide. Intermediate **32**, the key species from which the E1, E2, and $E1_{cb}$ pathways diverge, is endergonic by 9.2 kcal/mol. The E1 pathway, which involves loss of $OSPh_2$ to form carbocation **33**, requires 26.6 kcal/mol of free energy. This cation retains its hydrogen bond to the $(CF_3)_2CHO^-$ anion. Without this hydrogen bond the carbocation is endergonic by >50 kcal/mol. These thermodynamics provide strong evidence against an E1 dehydration mechanism.

We then searched for possible E2 and $E1_{cb}$ transition states from **32**. **TS1-*anti*** (Figure 2) is the lowest-energy transition

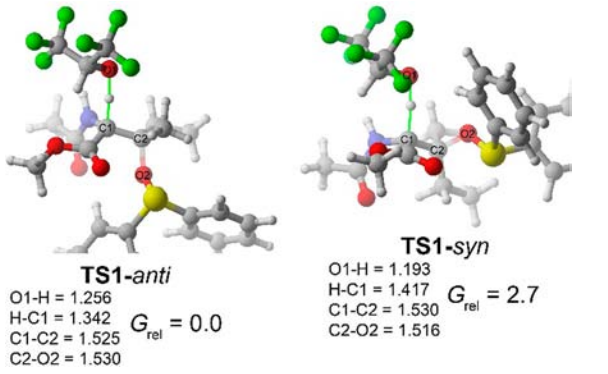


Figure 2. M06-2X *anti* and *syn* E2 transition states (distances reported in Å; phenyl groups partially obscured for clarity).

state, with $\Delta G^{\ddagger}$ = 13.9 kcal/mol. Inspection of **TS1-*anti*** indicates that it is either a highly asynchronous E2 transition state or an $E1_{cb}$ transition state. The nascent partial O1−H bond (1.26 Å) and the breaking C1−H bond (1.34 Å) are both highly advanced, while the C2−O bond (1.53 Å) is only stretched by 0.03 Å. While normal-mode vibrational analysis for **TS1-*anti*** did not show significant motion in the C2−O bond, IRC calculations suggest that **TS1-*anti*** connects to alkene **30** with no intermediate. We were unable to locate an $E1_{cb}$ transition state, and mapping of the entire potential energy landscape showed only **TS1-*anti*** and no local minimum for a carbanion intermediate. This suggests that **TS1-*anti*** is best interpreted as a highly asynchronous E2 transition state. A similar transition state was found by Itoh and Yamataka for the elimination reactions of 2-aryl-3-chloro-2-propanols.[27] We also considered that **TS1-*anti*** might be a merged transition state for E2 and $E1_{cb}$ pathways that could dynamically branch to alkene **30** and a carbanion.[28] We have discounted this possibility for two reasons. First, attempts to optimize a carbanion intermediate resulted in the formation of **30** and ejection of the $OSPh_2$ leaving group. Second, Itoh and Yamataka have shown that if the IRC follows an asynchronous E2 pathway, then all dynamics trajectories show only E2 products and no reaction pathway branching.

The observed stereoselectivity is likely the result of an *anti* transition state that is lower in energy than any of the possible *syn* transition states. Figure 2 shows the lowest-energy *syn* transition state that was located (**TS1-*syn***). It is not completely eclipsed and exhibits a moderate twist with a H−C1−C2−O2 dihedral angle of ~46°. The $\Delta G^{\ddagger}$ for **TS1-*syn*** is 16.6 kcal/mol, which is 2.7 kcal/mol higher in free energy than **TS1-*anti*** and qualitatively in accordance with the high stereoselectivity reported in Scheme 2 for the dehydration of **15**.

In summary, we have developed a concise and efficient route to *E*- and *Z*-ΔIle-containing peptides featuring an *anti*-selective dehydration of *β*-OHIle derivatives and a tandem Staudinger reduction/O → N acyl transfer. The former reaction is a rare example of a Martin sulfurane mediated tertiary alcohol dehydration that proceeds by a concerted asynchronous E2 mechanism. The latter process furnishes *E*- and *Z*-ΔIle-derived amides without recourse to backbone amide protection. It is

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anticipated that oxidation of the primary alcohols present in **24** and **27** will enable elongation of the peptide chains. The dehydration substrates are rapidly prepared via regioselective aminohydroxylation of trisubstituted alkenes. The stereoconvergent nature of the dehydration (i.e., the two diastereomers of **22b** and **25b** are converted into single alkene products) allows the use of a racemic aminohydroxylation. Density functional calculations indicate that the excellent stereoselectivity of the dehydration can be attributed to a highly asynchronous E2 *anti* pathway in which deprotonation is significantly more advanced at the transition state than C−O bond cleavage. This pathway is considerably lower in energy than all others that were examined (i.e., E2 *syn*, E1). Although no $E1_{cb}$ transition state was located, it is likely that the electron-withdrawing carboxylate group of the substrates is at least partially responsible for stabilizing the E2 *anti* transition state. This suggests that tertiary alcohols with vicinal electron-withdrawing groups might be good substrates for *anti*-selective dehydrations mediated by the Martin sulfurane. Due to the importance of ΔIle[1] and related bulky dehydroamino acids,[2−4] we envision many future applications of this strategy.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and NMR spectra for all new compounds, as well as descriptions of computational methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Ueoka, R.; Ise, Y.; Ohtsuka, S.; Okada, S.; Yamori, T.; Matsunaga, S. *J. Am. Chem. Soc.* **2010**, *132*, 17692. (b) Mackay, M. F.; Van Donkelaar, A.; Culvenor, C. C. J. *J. Chem. Soc., Chem. Commun.* **1986**, 1219. (c) Steinmetz, H.; Irschik, H.; Reichenbach, H.; Höfle, G. *Chem. Pept. Proteins* **1989**, *4*, 13. (d) Shimada, N.; Morimoto, K.; Naganawa, H.; Takita, T.; Hamada, M.; Maeda, K.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1981**, *34*, 1613. (e) Morimoto, K.; Shimada, N.; Naganawa, H.; Takita, T.; Umezawa, H.; Kambara, H. *J. Antibiot.* **1982**, *35*, 378. (f) Shiroza, T.; Ebisawa, N.; Furihata, K.; Endo, T.; Seto, H.; Otake, N. *Agric. Biol. Chem.* **1982**, *46*, 865. (g) Zenkoh, T.; Ohtsu, Y.; Yoshimura, S.; Shigematsu, N.; Takase, S.; Hino, M. *J. Antibiot.* **2003**, *56*, 694.

(2) (a) Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A.; Su, G. *Tetrahedron* **2004**, *60*, 11923. (b) Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A.; Su, G. *ARKIVOC* **2004**, No. iv, 59. (c) De Marco, R.; Greco, A.; Rupiani, S.; Tolomelli, A.; Tomasini, C.; Pieraccini, S.; Gentilucci, L. *Org. Biomol. Chem.* **2013**, *11*, 4316. (d) Tolomelli, A.; Baiula, M.; Belvisi, L.; Viola, A.; Gentilucci, L.; Troisi, S.; Dattoli, S. D.; Spampinato, S.; Civera, M.; Juaristi, E.; Escudero, M. *Eur. J. Med. Chem.* **2013**, *66*, 258.

(3) For a review, see: Bonauer, C.; Walenzyk, T.; König, B. *Synthesis* **2006**, 1.

(4) (a) English, M. L.; Stammer, C. H. *Biochem. Biophys. Res. Commun.* **1978**, *83*, 1464. (b) English, M. L.; Stammer, C. H. *Biochem. Biophys. Res. Commun.* **1978**, *85*, 780. (c) Shimohigashi, Y.; Stammer, C. H. *J. Chem. Soc., Perkin Trans. 1* **1983**, 803.

(5) (a) Stohlmeyer, M. M.; Tanaka, H.; Wandless, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 6100. (b) Grimley, J. S.; Sawayama, A. M.; Tanaka, H.; Stohlmeyer, M. M.; Woiwode, T. F.; Wandless, T. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8157.

(6) Shangguan, N.; Joullié, M. *Tetrahedron Lett.* **2009**, *50*, 6748.

(7) Kuranaga, T.; Sesoko, Y.; Sakata, K.; Maeda, N.; Hayata, A.; Inoue, M. *J. Am. Chem. Soc.* **2013**, *135*, 5467.

(8) (a) Tamamura, H.; Hori, T.; Otaka, A.; Fujii, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 577. (b) Yoshiya, T.; Kawashima, H.; Sohma, Y.; Kimura, Y.; Kiso, Y. *Org. Biomol. Chem.* **2009**, *7*, 2894. (c) Tailhades, J.; Gidel, M.-A.; Grossi, B.; Lécaillon, J.; Brunel, L.; Subra, G.; Martinez, J.; Amblard, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 117.

(9) (a) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327. (b) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003.

(10) For *anti* dehydrations of secondary alcohols (i.e., Thr and *β*-OHPhe), see: Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S. *Tetrahedron Lett.* **1998**, *39*, 9575.

(11) Harris, L.; Mee, S. P. H.; Furneaux, R. H.; Gainsford, G. J.; Luxenburger, A. *J. Org. Chem.* **2011**, *76*, 358.

(12) Ma, Z.; Naylor, B. C.; Loertscher, B. M.; Hafen, D. D.; Li, J. M.; Castle, S. L. *J. Org. Chem.* **2012**, *77*, 1208.

(13) Donohoe, T. J.; Bataille, C. J. R.; Gattrell, W.; Kloesges, J.; Rossignol, E. *Org. Lett.* **2007**, *9*, 1725.

(14) Masuri; Willis, A. C.; McLeod, M. D. *J. Org. Chem.* **2012**, *77*, 8480.

(15) (a) Sparling, B. A.; Moslin, R. M.; Jamison, T. F. *Org. Lett.* **2008**, *10*, 1291. (b) Wang, Z. *Comprehensive Organic Name Reactions and Reagents*; Wiley: Hoboken, NJ, 2010; pp 1841−1844.

(16) Kok, S. H.-L.; Lee, C. C.; Shing, T. K. M. *J. Org. Chem.* **2001**, *66*, 7184.

(17) In our earlier studies, low yields of ΔVal-containing products were obtained via the $Cu(OTf)_2$−EDC protocol. Accordingly, this method was not explored for the dehydration of **15**.

(18) (a) Soellner, M. B.; Tam, A.; Raines, R. T. *J. Org. Chem.* **2006**, *71*, 9824. (b) Kosal, A. D.; Wilson, E. E.; Ashfeld, B. L. *Chem.—Eur. J.* **2012**, *18*, 14444.

(19) (a) Crich, D.; Sana, K.; Guo, S. *Org. Lett.* **2007**, *9*, 4423. (b) Chen, W.; Shao, J.; Hu, M.; Yu, W.; Giulianotti, M. A.; Houghten, R. A.; Yu, Y. *Chem. Sci.* **2013**, *4*, 970.

(20) Lanigan, R. M.; Starkov, P.; Sheppard, T. D. *J. Org. Chem.* **2013**, *78*, 4512.

(21) Fang, G.-M.; Cui, H.-K.; Zheng, J.-S.; Liu, L. *ChemBioChem* **2010**, *11*, 1061.

(22) Details of the synthesis of **21a** and **21b** are found in the Supporting Information.

(23) Frisch, M. J., et al. *Gaussian 09*, revision B.01; Gaussian, Inc.: Wallingford, CT, 2009.

(24) (a) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215. (b) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157.

(25) Swart, M.; Solà, M.; Bickelhaupt, F. M. *J. Chem. Theory Comput.* **2010**, *6*, 3145.

(26) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378.

(27) Itoh, S.; Yamataka, H. *Chem.—Eur. J.* **2011**, *17*, 1230.

(28) Ess, D. H.; Wheeler, S. E.; Iafe, R. G.; Xu, L.; Celebi-Olcum, N.; Houk, K. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 7592.