Organic LETTERS

Letter

pubs.acs.org/OrgLett

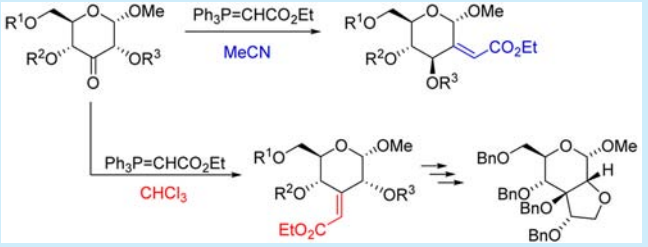
# Wittig Reaction: Domino Olefination and Stereoselectivity DFT Study. Synthesis of the Miharamycins' Bicyclic Sugar Moiety

Vasco Cachatra, Andreia Almeida, João Sardinha, Susana D. Lucas, Ana Gomes, Pedro D. Vaz, M. Helena Florêncio, Rafael Nunes, Diogo Vila-Viçosa, Maria José Calhorda,* and Amélia P. Rauter*

Centro de Química e Bioquímica, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Ed. C8, Piso 5, Campo Grande, 1749-016 Lisboa, Portugal

Supporting Information

**ABSTRACT:** 2-*O*-Acyl protected-D-*ribo*-3-uloses reacted with [(ethoxycarbonyl)methylene]triphenylphosphorane in acetonitrile to afford regio- and stereoselectively 2-(*Z*)-alkenes in 10−60 min under microwave irradiation. This domino reaction is proposed to proceed via tautomerization of 3-ulose to enol, acyl migration, tautomerization to the 3-*O*-acyl-2-ulose, and Wittig reaction. Alternatively, in chloroform, regioselective 3-olefination of 2-*O*-pivaloyl-3-uloses gave (*E*)-alkenes, key precursors for the miharamycins' bicyclic sugar moiety.




*α,β*-Unsaturated esters are often easily accessed by the reaction of the resonance-stabilized [(alkoxycarbonyl)methylene]-triphenylphosphoranes with carbonyl compounds, and the reagent is frequently used in sugar elongation and the synthesis of branched-chain sugars.[1] One of the major challenges encountered in keto sugar olefination is reaction stereocontrol. The direct and regioselective oxidation of position 2 may also be quite challenging, although the synthesis of a 2-ulose from a 3,4,6-tri-*O*-acetyl-protected sugar was successful with $Ac_2O$/DMSO[2] but with concomitant elimination of acetic acid to give an *α,β*-unsaturated carbonyl compound. In this work, we present a facile, regio- and stereoselective method for the Wittig reaction of 2-*O*-acyl-D-*ribo*-hexopyran-3-uloses with $Ph_3P{=}CHCO_2Et$ (**1**) that allows olefination either at position 2 or 3, depending on the solvent used, with the alkene (*E*)- or (*Z*)-configuration being controlled by the bulky acyl group vicinal to the carbonyl functionality.

Carbohydrates that embody (ethoxycarbonyl)methylene have been successfully used by us as scaffolds for the generation of bicyclic, sugar-fused, five-membered *α,β*-unsaturated lactones.[3] However, attempts to convert such compounds into the bicyclic miharamycin sugar moiety (Figure 1, A and B) have failed, affording instead the epimer of the chiral secondary alcohol at the newly formed tetrahydrofuran ring. This antibiotic displays a potent activity against *Pyricularia oryzae*, a fungus which causes the rice blast disease, which is now considered a bioterrorism agent. Miharamycins were isolated 40 years ago from *Streptomyces miharaensis* SF-489.[4] Their bicyclic sugar residue has been synthesized by samarium iodide cyclization of a 2-*O*-propargyl-3-ulose, followed by ozonolysis and stereoselective reduction.[5] Focusing our attention on these antibiotics, our group has developed the first synthesis of the miharamycins' sugar epimer at the sugar-fused tetrahydrofuran ring[6] and that of the structurally related antibiotic amipurimycin sugar residue, embodying a branched chain at C-3 of a 4-deoxypyranose.[7] The first total synthesis of the miharamycins' core was also reported by us in 2008.[8] The miharamycins' bicyclic sugar moiety is also a structural feature of nucleosides (Figure 1, C) that have shown a potent and selective inhibition of butyrylcholinesterase (BChE), an enzyme whose concentration increases considerably in later Alzheimer's disease stages.[9] BChE has been found in senile plaques, and the recently reported association of the BChE locus with A*β* deposition merits further investigation and may have significant implications for therapeutic treatment.[10]

Hence, we were motivated to explore the utility of Wittig olefination for the efficient synthesis of this type of compound. We disclose now the first stereoselective and facile synthesis of such bicyclic sugars starting from a 2-*O*-pivaloyl-3-ulose.

The Wittig reaction of 3-uloses differing in their 2,4,6-*O*-protection was carried out with **1** in chloroform or acetonitrile under conventional or microwave-assisted heating, and the results are summarized in Table 1.

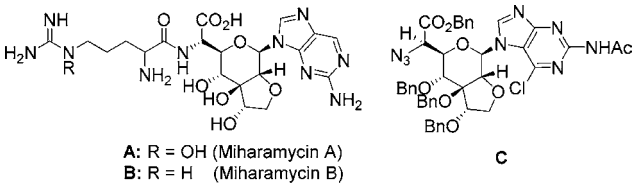



**Figure 1.** Miharamycins (A, B) and related BChE-selective inhibitor nucleoside (C).

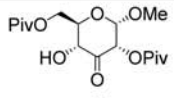
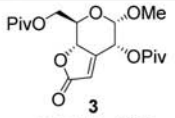
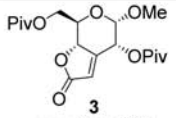
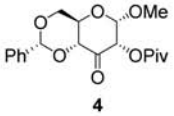
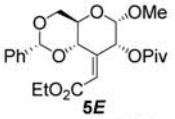
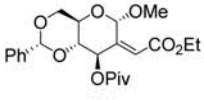
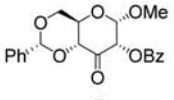
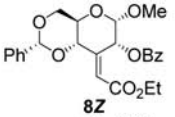
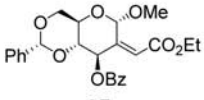
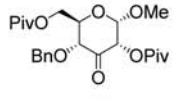
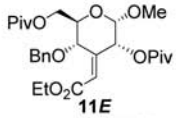
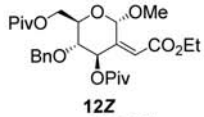
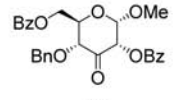
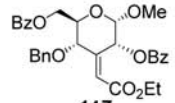
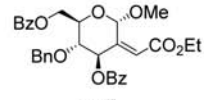
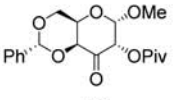
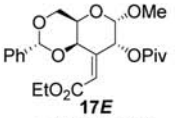
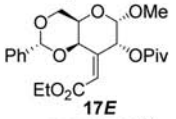
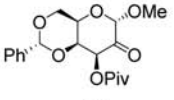
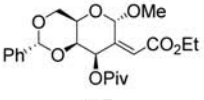
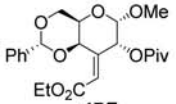
**Received:** October 1, 2015
**Published:** November 9, 2015





DOI: 10.1021/acs.orglett.5b02849
*Org. Lett.* 2015, 17, 5622−5625

**Table 1. Wittig Reaction of 3-/2-Uloses with Phosphorane 1 by Conventional and Microwave-Assisted Heating**[a]

| ulose | Wittig product | |
|---|---|---|
| | $CHCl_3$ | MeCN |
|  **2** |  **3** conv 6 h, 90% MW 30 min, 87% |  **3** conv 1 h, 90% MW 10 min, 85% |
|  **4** |  **5*E*** conv 6 h, 74% MW 6 h, 72% (*E*/*Z* 5:1) |  **6*Z*** conv 3 h, 65% MW 10 min, 63% |
|  **7** |  **8*Z*** conv 6 h, 61% MW 10 min, 63% (*Z*/*E* 3:1) |  **9*Z*** conv 3 h, 60% MW 10 min, 64% |
|  **10** |  **11*E*** conv 3 d, 65% MW 3 d, 67% |  **12*Z*** conv 6 h, 76% MW 1 h, 79% (*Z*/*E* 4:1) |
|  **13** |  **14*Z*** conv 3 d, 61% MW 1 d, 64% |  **15*Z*** conv 6 h, 70% MW 1 h, 74% (*Z*/*E* 7:1) |
|  **16** |  **17*E*** conv 4 h, 82% MW 2 h, 79% |  **17*E*** conv 4 h, 79% MW 10 min, 75% |
|  **18** |  **19*Z*** conv 4 h, 69% MW 2 h, 65% (*Z*/*E* 7:1) |  **17*E*** conv 4 h, 68% MW 10 min, 66% |

[a]All reactions were performed under reflux conditions. Key: conv, conventional heating; MW, microwave-assisted heating. *E*/*Z* ratio is given when both isomers are detected in the $^1$H NMR spectrum of the reaction mixture.

The contribution of the protecting group functionality, vicinal to the carbonyl group, on the reaction outcome was investigated. 3-Uloses bearing a bulky *O*-pivaloyl or a *O*-benzoyl group at position 2 and exhibiting a free hydroxy or a free benzyloxy group at position 4, or a 4,6-*O*-benzylidene group were evaluated (for their synthesis, in good yields, see the Supporting Information). Previously, it has been observed that Wittig reaction of phosphorane **1** with 4-deoxy-2-*O*-pivaloyl-3-ulose in chloroform afforded exclusively the (*E*)-alkene in high yield.[7] We have found that when the equatorial H-4 is replaced by a hydroxy group (ulose **2**), intramolecular cyclization is favored to give **3** in 90% yield. The latter compound embodies a five-membered lactone fused to positions 3 and 4, suggesting that the Wittig reaction stereoselectivity proceeded toward the (*E*)-alkene, which underwent cyclization both in chloroform and acetonitrile. However, the reaction time was considerably reduced when the solvent was acetonitrile, resulting from the increased solvent polarity and higher reaction temperature. Reaction of *ribo*-3-uloses **4**, **7**, **10**, and **13** (differing in the 2,4,6-protecting group pattern) with **1** in acetonitrile resulted in C2-olefination. The major alkenes formed had a configuration in which the ethoxycarbonyl group occupied the less sterically congested side of the double bond, defined as the (*Z*)-configuration by the Cahn, Prelog, and Ingold rules,[11] in the presence of either the benzoyl or the pivaloyl protecting groups. Solvation of the ylide in acetonitrile favored keto−enol tautomerization of 3-uloses, followed by intramolecular acyl migration and tautomerization that gave the 2-ulose, which reacted *in situ* with the ylide. The resulting Wittig products had the substituent at position 3 in the equatorial position. This gives rise to coupling constants $^3J_{3,4}$ with values between 9.2 and 10.3 Hz, characteristic of a *trans* diaxial coupling. The insertion of the double bond at position 2 was confirmed by the presence of H-1 at chemical shifts $\delta$ 6.28−6.48 as a singlet; the signal of H-3 appeared either as a broad d or a dd when coupling constant $^4J_{2',3}$ with the olefinic proton was detected. The proposed double-bond configuration was assigned by NOESY, mainly based on the correlation detected between H-2′ and protons of the substituent at position 3, and that of H-1 with the methylene of the ethoxycarbonyl group. Interestingly, the reaction time of this domino reaction is much lower than that of the direct olefination at position 3 in chloroform, in particular for the reaction of uloses **10** and **13**, whose reaction time decreased from 3 days for 3-olefination to 6 h.

The stereochemical input of position 4 was investigated by conducting the Wittig reaction with the D-*xylo*-3-ulose **16**. Only 3-olefination took place both in chloroform and acetonitrile with the same reaction time and similar yield, possibly due to hindrance caused by the 4,6-benzylidene group. However, domino olefination of D-*lyxo*-ulose **18**, which embodies the carbonyl group at position 2, took place in acetonitrile to afford, in 68% yield, the 3-alkene **17*E***, where the substituent at position 2 was in equatorial orientation. As expected, olefination in chloroform led to the 2-alkene **19*Z*** as the major reaction product.

When reactions were carried out under microwave irradiation, reaction stereo- and regioselectivity did not change as shown by comparable product yields, but reaction times decreased considerably, with the exception of direct 3-olefination of uloses **4** and **10** in chloroform, for which reaction time was maintained when compared to conventional heating. In chloroform, Wittig reaction of 3-uloses always afforded 3-alkenes as major products, their configuration depending on the acyl protecting group at position 2. The bulky pivaloyl group forces the formation predominantly of (*E*)-alkenes (compounds **5*E***, **11*E***, **17*E***), as expected for reactions with stabilized ylides,[12] while in the presence of 2-*O*-benzoyl protection, the major alkene has the (*Z*)-configuration (compounds **8*Z*** and **14*Z***). DFT calculations [Gaussian09, PBE0/6-31G**($CHCl_3$)] were performed in order to gain



DOI: 10.1021/acs.orglett.5b02849
*Org. Lett.* 2015, 17, 5622−5625

insight into the factors governing this stereoselectivity. We addressed the reaction of the benzylidene-protected 3-uloses **4** and **7** with phosphorane **1** to afford alkenes **5*E*** and **8*Z***, respectively. In the accepted mechanism,[12] salt-free Wittig reactions usually proceed through [2 + 2 + 0]-cycloaddition to form an oxaphosphetane intermediate followed by pseudorotation around phosphorus and stereospecific [2 + 2 + 0]-cycloreversion to yield the alkene and phosphine oxide. Extensive computational evidence supports this mechanism for aldehyde reactions.[12−14] The reaction that leads to the formation of alkene **8*Z*** (Figure 2 and Figure S1) starts with **7** and **1** approaching (**7***) to form the oxaphosphetane intermediate **OP1**. The reagents can approach with different orientations, the stereochemistry of the product alkene being determined by the relative stability of the cycloaddition transition states, in agreement with the model first proposed by Vedejs and co-workers.[12] The lower transition-state energy for **TS1** (29.5 kcal mol$^{-1}$) corresponds to the concerted addition of the ylide to the ulose when it proceeds from the less hindered upper face of the sugar ring[15] and also leads to the lowest energy intermediate **OP1**. C−C bond formation (1.920 Å) is well advanced, while the P−O distance (2.996 Å) characterizes a weak interaction, conferring an asynchronous nature to **TS1**. A weak C−H···O hydrogen bond (2.008 Å, 144.2°) between the carbonyl oxygen and one carbon atom of a phenyl group stabilizes the slightly puckered four-atom cycle (PCCO = −13.9°). **OP1** converts into **OP2** by exchanging an apical oxygen with an apical carbon with a barrier of 3.4 kcal mol$^{-1}$ (**TSOP**), preceded by small rotation of substituents (**OP1***). This low energy conversion is not clear in the literature,[12−14,16] and **TSOP** (only calculated for this reaction pathway) is the first reported transition state that is effectively connected to the two intermediates **OP1** and **OP2**. The latter undergoes cycloreversion (**8***), decomposing into alkene **8*Z*** and triphenylphosphine oxide via another transition state (**TS2**), with a low barrier of ∼5.3 kcal mol$^{-1}$. The formation of alkene **8*E*** follows an analogous pathway (Figure S3), but both transition states have higher energies (32.1 and 31.3 kcal mol$^{-1}$ for **TS1** and **TS2**, respectively), in agreement with the observed stereoselectivity. Interestingly, alkene **8*Z*** is not the thermodynamically favored product, as its energy is higher by 0.9 kcal mol$^{-1}$. On the other hand, the energy profiles for the conversion of 2-*O*-pivaloyl-3-ulose **4**, into alkenes **5*Z*** and **5*E*** (Figures S4 and S5), reveal that the observed product **5*E*** is formed with a barrier of 32.5 kcal mol$^{-1}$ (**TS1**), while the other (**5*Z***) requires 35.0 kcal mol$^{-1}$. **5*E*** is also the thermodynamically favored product. These calculations pinpoint a key role for steric effects in controlling the stereoselectivity of Wittig reactions involving stabilized ylides and uloses bearing acyl protection vicinal to the carbonyl functionality.

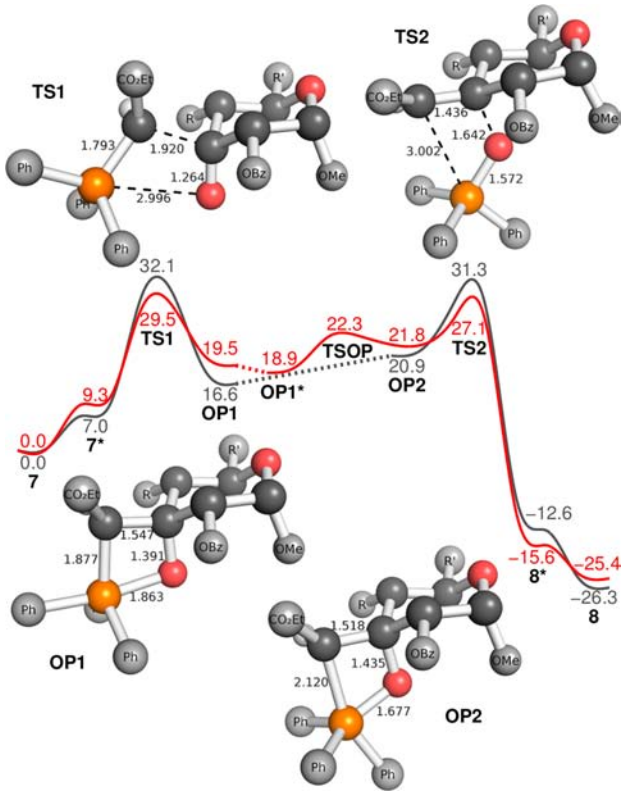
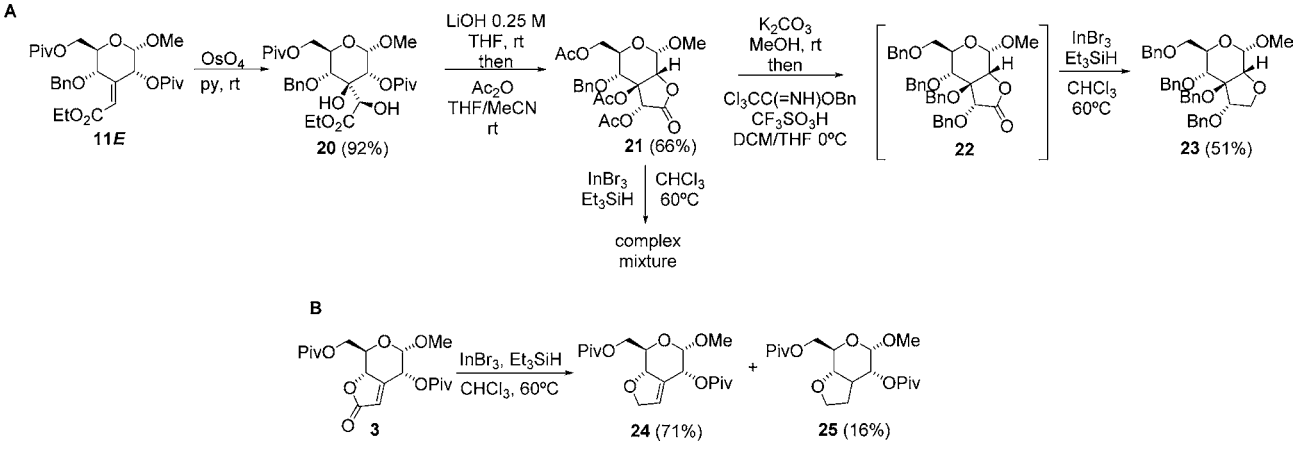



**Figure 2.** Energy profiles for the conversion of 2-*O*-benzoyl-3-ulose **7** into alkenes **8*Z*** (in red) and **8*E*** (in gray) (Δ*G* in kcal mol$^{-1}$ and distances in Å). Selected optimized geometries (truncated for clarity) are shown for the lower energy path.

Pursuing our studies to achieve an alternative strategy for the synthesis of the miharamycin bicyclic sugar moiety, we outline here an efficient and easy to run methodology involving osmylation of the (*E*)-alkenes type **5** or **11** for generating key

**Scheme 1. Miharamycins' Bicyclic Sugar Moiety Synthesis**






DOI: 10.1021/acs.orglett.5b02849
*Org. Lett.* 2015, 17, 5622−5625

precursors with the stereochemistry appropriate for the miharamycin tetrahydrofuran secondary alcohol.

As shown for compound **11*E***, double-bond osmylation was followed by cyclization to lactone **21** by reaction with LiOH and acetylation of the crude product (Scheme 1A). Reductive deoxygenation of lactone **21** with trichlorosilane, $BH_3$−DMS/$NaBH_4$, and $Et_3SiH/TiCl_4$−TMSOTf was attempted. However, only $Et_3SiH$ in the presence of catalytic $InBr_3$ succeeded to give the target compound. This method, developed by Sakai and co-workers[17] and herein applied to carbohydrate templates for the first time, seems to be promising for reducing this type sugar-fused lactone. Preliminary studies on the readily available bicyclic lactone **3** afforded, after 45 min, the reduced unsaturated lactone **24** in 71% yield and compound **25**, bearing the fully reduced tetrahydrofuran ring, in 16% yield, both keeping the pivaloyl group in the structure (Scheme 1B). However, when the system was applied to lactone **21**, a complex reaction mixture was obtained. The target molecule **23** was synthesized by replacing the acetyl by benzyl groups. This transformation was carried out by treatment of **21** with a methanolic solution of $K_2CO_3$ for deprotection, followed by benzylation with benzyl trichloroacetimidate. Reductive deoxygenation of **22** assisted by $Et_3SiH$ and $InBr_3$ afforded the fully protected miharamycins' sugar moiety **23** in 51% yield over three steps (Scheme 1A).

Spectroscopic and analytical data are in full agreement with those predicted for structure **23**, which can be used, after deprotection/orthogonal protection, as starting material for the miharamycins' total synthesis,[8] making this synthetic approach a valuable alternative to the samarium iodide-based methodology previously described.[5]

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02849.

Detailed experimental procedures, compound characterization by physical, spectroscopic, and HRMS data, and copies of $^1H$ and $^{13}C$ NMR spectra of new compounds (PDF)

Computational details, full results for the energy profiles, and geometrical parameters (PDF)

Coordinates for the optimized intermediates and transition states (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Authors

*E-mail: aprauter@fc.ul.pt.
*E-mail: mjc@ciencias.ulisboa.pt.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank Dr. Gerry Moss (Queen Mary University of London) for advice regarding the compounds' IUPAC systematic names. Fundação para a Ciência e a Tecnologia is gratefully acknowledged for financial support of the project UID/MULTI/00612/2013 and for Ph.D. grants for V.C. (SFRH/BD/90359/2012) and D.V.-V. (SFRH/BD/81017/2011).

## ■ DEDICATION

Dedicated to the memory of Prof. Dr. Derek Horton.

## ■ REFERENCES


(1) Cachatra, V.; Rauter, A. P. *Curr. Org. Chem.* **2014**, *18*, 1731.

(2) Xavier, N. M.; Goulart, M.; Neves, A.; Justino, J.; Chambert, S.; Rauter, A. P.; Queneau, Y. *Bioorg. Med. Chem.* **2011**, *19*, 926.

(3) (a) Xavier, N. M.; Rauter, A. P. *Org. Lett.* **2007**, *9*, 3339. (b) Xavier, N. M.; Silva, S.; Madeira, P. J. A.; Florêncio, M. H.; Silva, F. V. M.; Justino, J.; Thiem, J.; Rauter, A. P. *Eur. J. Org. Chem.* **2008**, *2008*, 6134. (c) Xavier, N. M.; Madeira, P. J. A.; Florêncio, M. H.; Rauter, A. P. *Eur. J. Org. Chem.* **2009**, *2009*, 4983.

(4) Tsuruoka, T.; Yumoto, H.; Ezaki, N.; Niida, T. *Sci. Rep. Meiji Seika Kasha* **1967**, *9*, 1.

(5) Fairbanks, A. J.; Sinaÿ, P. *Synlett* **1995**, *1995*, 277.

(6) (a) Rauter, A.; Ferreira, M.; Borges, C.; Duarte, T.; Piedade, F.; Silva, M.; Santos, H. *Carbohydr. Res.* **2000**, *325*, 1. (b) Rauter, A. P.; Oliveira, O.; Canda, T.; Leroi, E.; Ferreira, H.; Ferreira, M. J.; Ascenso, J. A. *J. Carbohydr. Chem.* **2002**, *21*, 257.

(7) Rauter, A. P.; Fernandes, A. C.; Czernecki, S.; Valery, J.-M. *J. Org. Chem.* **1996**, *61*, 3594.

(8) Marcelo, F.; Jiménez-Barbero, J.; Marrot, J.; Rauter, A. P.; Sinaÿ, P.; Blériot, Y. *Chem. - Eur. J.* **2008**, *14*, 10066.

(9) Marcelo, F.; Silva, F. M. S.; Goulart, M.; Justino, J.; Sinaÿ, P.; Blériot, Y.; Rauter, A. P. *Bioorg. Med. Chem.* **2009**, *17*, 5106.

(10) Ramanan, V. K.; Risacher, S. L.; Nho, K.; Kim, S.; Swaminathan, S.; Shen, L.; Foroud, T. M.; Hakonarson, H.; Huentelman, M. J.; Aisen, P. S.; Petersen, R. C.; Green, R. C.; Jack, C. R.; Koeppe, R. A.; Jagust, W. J.; Weiner, M. W.; Saykin, A. J. Alzheimer's Disease Neuroimaging Initiative Mol. *Mol. Psychiatry* **2014**, *19*, 351.

(11) Cahn, R. S.; Ingold, C.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5* (4), 385.

(12) Byrne, P. A.; Gilheany, D. G. *Chem. Soc. Rev.* **2013**, *42*, 6670.

(13) (a) Robiette, R.; Richardson, J.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 13468. (b) Robiette, R.; Richardson, J.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2006**, *128*, 2394.

(14) Stępień, M. *J. Org. Chem.* **2013**, *78*, 9512.

(15) Addition of the ylide from the opposite face of the pyranose ring requires a significantly higher (~8.5 kcal $mol^{-1}$) activation barrier (see Figure S2, Supporting Information).

(16) García López, J. G.; Ramallal, A. M.; González, J.; Roces, L.; García-Granda, S.; Iglesias, M. J.; Oña-Burgos, P.; Ortiz, F. L. *J. Am. Chem. Soc.* **2012**, *134*, 19504.

(17) Sakai, N.; Moriya, T.; Konakahara, T. *J. Org. Chem.* **2007**, *72*, 5920.




DOI: 10.1021/acs.orglett.5b02849
*Org. Lett.* 2015, 17, 5622−5625