Diels-Alder reaction of two green chiral precursors. Approach to natural product like structures

Gonzalo Carrau, Nicolas Veiga, Leopoldo Suescun, Germán F. Giri, Alejandra G. Suárez, Rolando Spanevello, David González

PII: S0040-4039(16)31188-1
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.09.031
Reference: TETL 48101

To appear in: *Tetrahedron Letters*

Received Date: 21 July 2016
Revised Date: 29 August 2016
Accepted Date: 7 September 2016

Please cite this article as: Carrau, G., Veiga, N., Suescun, L., Giri, G.F., Suárez, A.G., Spanevello, R., González, D., Diels-Alder reaction of two green chiral precursors. Approach to natural product like structures, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.09.031

Diels-Alder reaction of two green chiral precursors. Approach to natural product like structures.

Gonzalo Carrau,[a] Nicolas Veiga,[b] Leopoldo Suescun,[c] Germán F. Giri,[d] Alejandra G. Suárez,[d] Rolando Spanevello,[d] and David González*[a]

a) Departamento de Química Orgánica, Fac. de Química, UdelaR, Montevideo - Uruguay.

b) Departamento Estrella Campos, Fac. de Química, UdelaR, Montevideo - Uruguay.

c) Cryssmat-Lab, Cátedra de Física, DETEMA, Fac. de Química, UdelaR, Montevideo - Uruguay.

d) IQUIR, UNR, Rosario – Argentina.

Corresponding author's e-mail address: davidg@fq.edu.uy

Abstract: *Diels-Alder cycloaddition between an enantiomerically pure protected cis-ciclohexadienediol metabolite and optically pure levoglucosenone derived from cellulose gave rise to complex pentacyclic natural product like structures in a chemically succinct process. The adducts were fully characterized and the observed results were in accord with theoretical calculations performed on the possible course of the reaction.*

Introduction

The quest for strategies to rapidly build structural diversity, often targeting complex chiral molecules that resemble natural products, has emerged as route for the discovery of new bioactive molecules.[1] These structures are often called *natural product like (NPL)* compounds and typically comprise molecules with several rings and stereochemically defined chiral centers and double bonds. The interest in NPL compounds becomes relevant when they are constructed by short synthetic sequences. In that fashion, NPL compounds could incorporate the advantages of natural products such as complexity and diversity, along with the benefits of typical synthetic pharmaceutical molecules, such as the ease of preparation and structural modification.[2] In addition, the gain of considering NPL compounds among potential drug candidates is increased when they are accessible via green routes or renewable starting materials.[3]

Our groups have a tradition of working in green chemistry and biocatalysis. The Uruguayan group has a tradition in biocatalysis and the exploitation in synthesis of homochiral cyclohexadiene diols like compound **1** (Scheme 1) obtained by microbial oxidation of aromatics.[4] These metabolites have been utilized worldwide for the synthesis of alkaloids, inositols, prostaglandins, and a wide array of natural products and unnatural analogues. The results of these efforts have been reviewed extensively,[5] and to date cyclohexadiene diols are considered among the most versatile chiral precursors.

The group in Argentina has made several contributions to synthetic methodology working in the preparation and modification of levoglucosenone (compound **3**, Scheme 1), a chiral starting material obtainable from pyrolysis of cellulose. The pyrolytic conversion of biomass into useful chemicals,[6] has resulted in synthetic applications of levoglucosenone (1,2-anhydro-3,4-dideoxy-β-D-glycero-hex-3-enopyranos-2-ulose, **3**) as a chiral building block for the development of new methods for asymmetric synthesis.[7] This versatile and easily available synthon from the carbohydrate family can be produced in enantiomeric pure form by

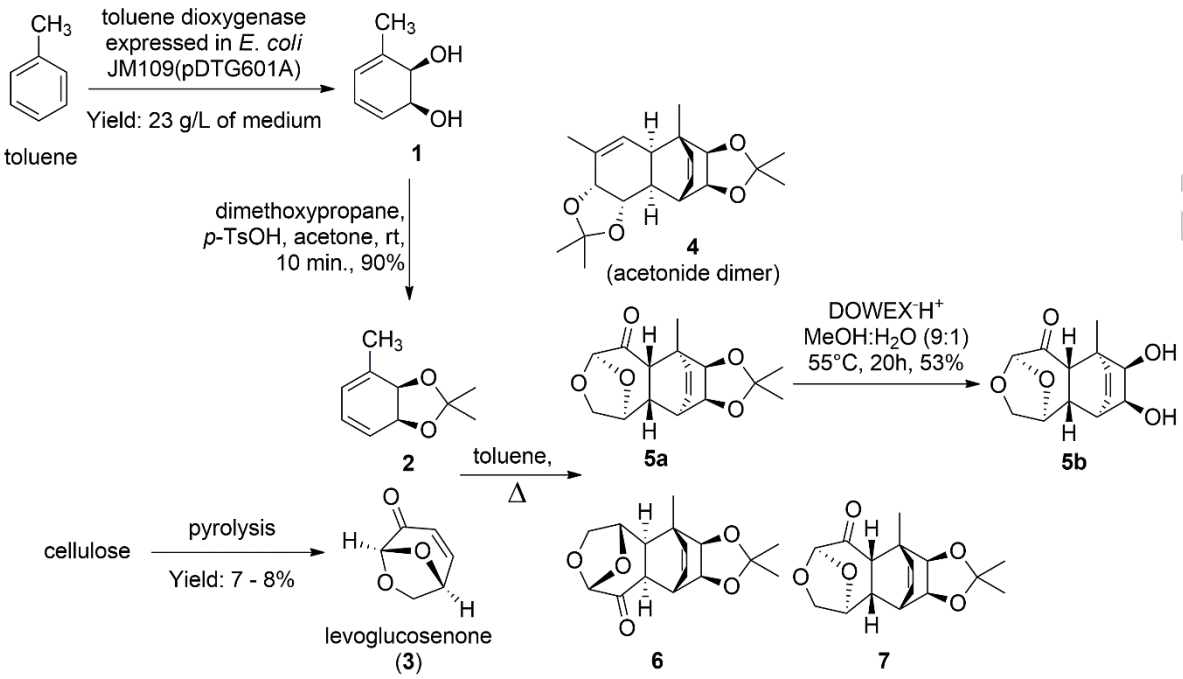
conventional pyrolysis of cellulose containing materials,[8] such as waste paper, but also by microwave (MW) irradiation of microcrystalline cellulose.[9]

The Diels-Alder reaction has been widely applied to the total syntheses of natural products. The reaction itself has become a valuable tool in the development of synthetic, mechanistic, and theoretical concepts, and this important role could be attributed to its remarkable regio- and stereoselectivities.[10] This versatility provides a powerful means to challenge the construction of complex molecules.[11] Both levoglucosenone and cyclohexadiene diols are superb partners in Diels-Alder reactions. Levoglucosenone has been studied as dienophile and cyclohexadiene diol derivatives have been used in DA and hetero DA reactions as relevant dienes.[12] Interestingly, diol derivatives can also react as dienophiles as it can be noted in the rapid dimerization of the corresponding acetonides.[12c, 13] Along these lines we decided to joint efforts and test the Diels-Alder reaction of levoglucosenone (**3**) and the acetonide derivative **2** obtained from (1*S*,2*R*)-3-methylcyclohexa-3,5-diene-1,2-diol (**1**), by reaction with dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid.

Results and discussion

Chemical reactions

The presence of four chiral centers and a distinguished high degree of face selectivity in both partners (**2** and **3**) suggested that they might render adducts of elevated molecular complexity with a good degree of stereoselectivity. In fact, this Diels-Alder reaction could afford up to eight stereoisomers depending on the facial approach and orientation of the partners. Therefore, we can have *endo* and *exo* products, *ortho* and *meta* Diels-Alder adducts, and finally α and β approaches (α refers to the approach of levoglucosenone from the α face of the diene) (Scheme 1).



Scheme 1. Reaction of levoglucosenone (**3**) and acetonide **2**.

Reaction description and NMR analysis.

Diels-Alder cycloaddition was initially performed in toluene under reflux conditions, and three products where obtained (Table 1, entry 1). One of them was assigned to the acetonide dimer **4**[14] (24%) and the main product was assigned to compound **5a** (30%) while isomeric adduct **6** accounted for only 5%. NMR analysis of the main product (**5a**) clearly showed that the *ortho* adduct was obtained (confirmed by HMBC experiment), but the data were not enough to fully discriminate between the four possible isomers. Removing of the acetonide group under acidic conditions rendered crystalline diol **5b**, and its structure was determined by X-Ray diffraction analysis.[15] As illustrated in Figure 1, the levoglucosenone must have approached from de concave β face of the diene, and the transition state corresponded to an *endo* adduct. The structure of the minor product **6** was also determined by X-ray diffraction analysis.[16] Increasing the reaction temperature to 200 °C and adding an excess of levoglucosenone repressed the formation of the dimer and increased the

yield of **5a** to 70%. However, in these conditions 5% of a third adduct (**7**) was detected (Entry 3).

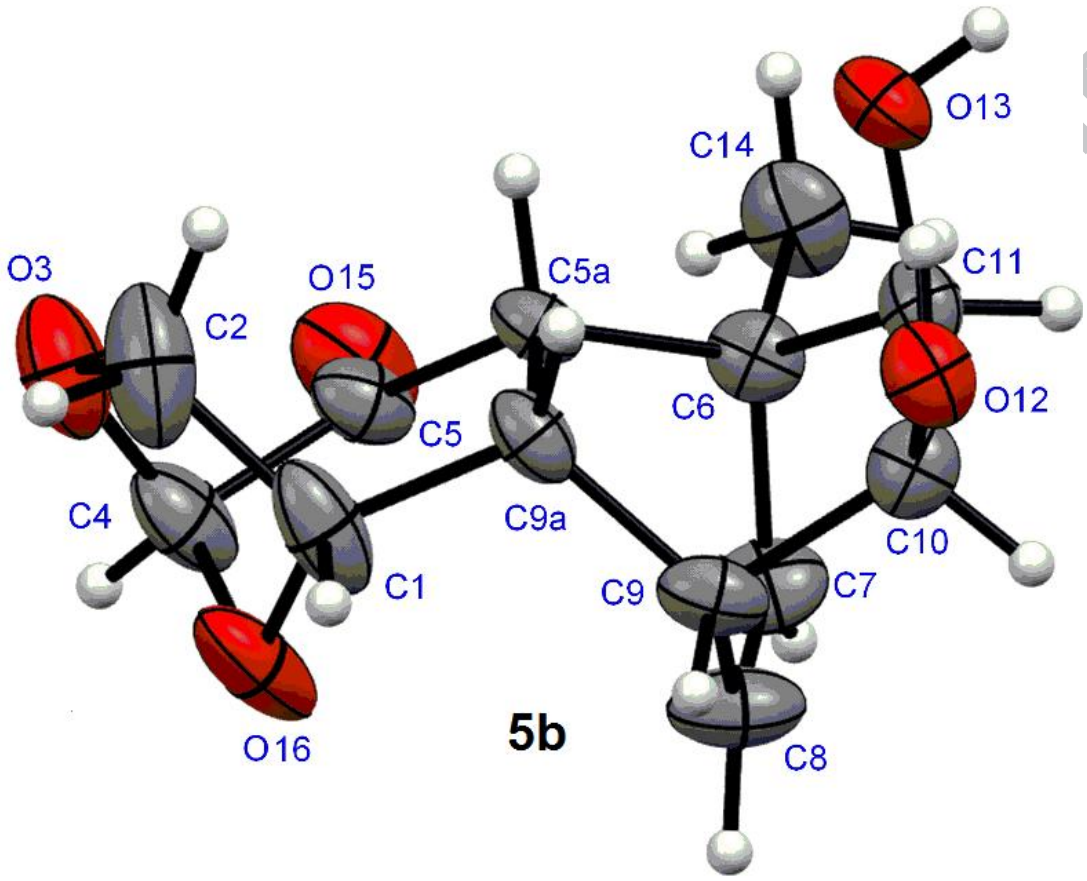


Figure 1. Crystal structure of diol **5b** derived from adduct **5a**.

It is noteworthy that acetonide **2** generally undergoes Diels-Alder reaction from the convex α face ruled by steric effects of the acetonide group, and if the β product is obtained, it is generally in very low yield.[14, 17] As our result was unexpected, theoretical calculations were done in order to explain the outcome of the reaction.

Table 1. Tested conditions for the Diels-Alder reaction.

Entry	Temp. (°C)	Time (h)	Eq. of **3**	Product (% yield)
1	reflux	48	1.1	**4** (24), **5a** (30), **6** (5)
2	200	10	1.1	**4** (8), **5a** (42), **6** (15), **7** (6)
3	200	3	6	**4** (traces), **5a** (70), **6** (18), **7** (5)
4	reflux	3	6	**4** (traces), **5a** (64), **6** (16), **7** (10).

Computational studies

In order to shed light on the experimentally observed stereoselectivity, we have performed quantum chemical calculations of the Diels–Alder reaction. High level ab initio and B3LYP/6-31G(d) DFT methods have proved to give excellent results for energy barrier estimation of cycloaddition reactions.[18] Besides, these electronic structure calculations have previously been used to predict stereospecificity of different Diels–Alder reactions of cyclic dienes with cyclic dienophiles.[19] Therefore, we have used the B3LYP/6-31+G(d,p) levels of theory to investigate the potential energy surface (PES), by means of the thermodynamic and structural characterization of the transition structures and related minima.

The optimized geometries of the reactants and the major product, as well as the predicted reaction profiles for the eight potential cycloadditions, are shown in Figure 2. In total accordance with the experimental data, the computational results predict that the β-*endo-ortho* product **5a** is the most kinetically favored of all the possibilities, with a free energy difference with the next most stable transition state of 0.61 kcal/mol (toluene boiling temperature). Moreover, there are two other products whose formation is also preferred from a kinetic viewpoint: α-*endo-meta* (**6**) and α-*exo-ortho* (**7**). Remarkably enough, we were able to detect and characterize both molecules as minor by-products of the Diels–Alder reaction under the applied experimental conditions. These results prove the satisfactory performance of the computational model, and suggest a kinetic control of the reaction.

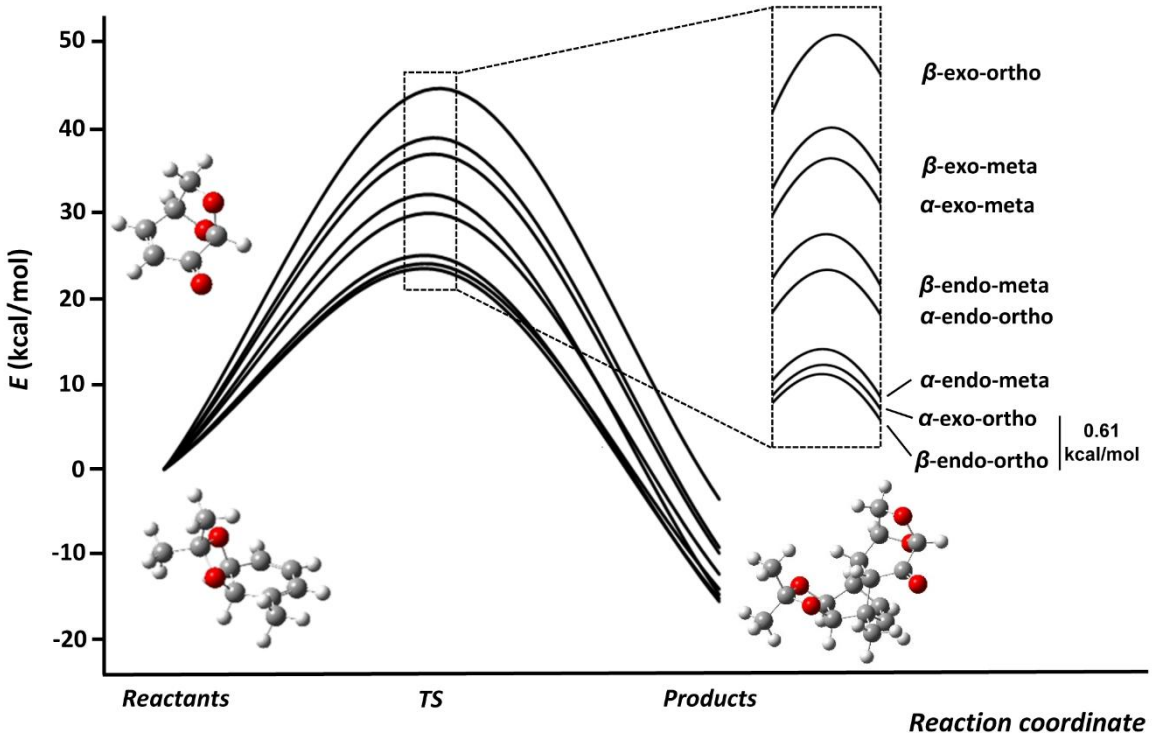


Figure 2. Predicted reaction profiles for the formation of the eight Diels Alder adducts. The calculated DFT geometries for the reactants and the obtained product are also depicted. The free energy difference between the two most stable transition states at the toluene boiling temperature is shown in kcal/mol. Color code: C (grey), H (white), O (red).

Another interesting point is the fact that the activation energies ($\Delta E^{\ddagger}$) for the cycloadditions are significant (23 – 45 kcal/mol). This explains the use of high temperatures to allow the reactants to overcome the high-energy activation barrier, brought about mainly by a substantial structural deformation at the transition state. The combination between this geometrical distortion and the attractive and repulsive interactions at the transition state seems to be quite different for the various cycloadditions, since the activation energies span a range of 22 kcal/mol.

Conclusions

These experiments demonstrated that the Diels-Alder coupling of diene diol metabolites arisen from substituted benzenes and levoglucosenone derived from cellulose is a valid tool to construct complex natural product like structures with high stereoselectivity. The whole procedure is a short and efficient process that comprises four steps: biocatalysis, pyrolysis, cycloaddition and hydrolysis. The three-dimensional structures of the major product and two minor isomers were confirmed beyond doubt by spectrometric methods (X-Ray diffraction and high field NMR analysis). Crystal structures were solved for diol **5b** (derived from the main product **5a**) and for **6**, while the structure of the third product (adduct **7**) was confirmed by comparison of predicted and experimental coupling constants values. Moreover, the experimental results were found to be in full agreement with a theoretical analysis of the reaction course. The three isolated isomers correspond to the ones predicted to be formed following the most favorable pathway of approach between the cycloaddition partners. Detailed experimental procedures as well as complete characterization data including X-Ray and NMR spectra for all compounds is provided in the Supplementary Material.

Acknowledgements

Funding agencies: PEDECIBA, CSIC (Heavy Equipment Program), ANII (Project FCE-6669 and PR_EQC_2012_7), UNR, CONICET and Agencia Nacional de Promoción Científica y Tecnológica. GC acknowledges ANII and CAP for a doctoral fellowship (POS_NAC_2013_1_11296) and GFG thanks CONICET for a doctoral fellowship. The authors acknowledge Horacio Pezaroglo, Veronica Martinez and Prof. Guillermo Moyna for recording NMR spectra, and Victoria Panzl, David Menchaca and Prof. Alejandra Rodriguez for recording HRMS spectra.

References and notes

1. (a) Zhang, J.; Wu, J.; Hong, B.; Ai, W.; Wang, X.; Li, H.; Lei, X., *Nat. Commun.* **2014,** *5*, 4614; (b) Yu, L. G.; Ni, T. F.; Gao, W.; He, Y.; Wang, Y. Y.; Cui, H. W.; Yang, C. G.; Qiu, W. W., *Eur. J. Med. Chem.* **2015,** *90*, 10-20; (c) Qiu, G.; Wu, J., *Synlett* **2014,** *25*; (d) Petersen, R.; Le Quement, S. T.; Nielsen, T. E., *Angew. Chem., Int. Ed.* **2014,** *53*, 11778-11782; (e) Grossmann, A.; Bartlett, S.; Janecek, M.; Hodgkinson, J. T.; Spring, D. R., *Angew. Chem., Int. Ed.* **2014,** *53*, 13093-13097; (f) Denizot, N.; Pouilhès, A.; Cucca, M.; Beaud, R.; Guillot, R.; Kouklovsky, C.; Vincent, G., *Org. Lett.* **2014,** *16*, 5752-5755; (g) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A., *Angew. Chem., Int. Ed.* **2009,** *48*, 104-109; (h) Appendino, G.; Tron, G. C.; Jarevång, T.; Sterner, O., *Org. Lett.* **2001,** *3*, 1609-1612; (i) Nicolaou, K.; Pfefferkorn, J.; Roecker, A.; Cao, G.-Q.; Barluenga, S.; Mitchell, H., *J. Am. Chem. Soc.* **2000,** *122*, 9939-9953.
2. (a) Liu, Y.; Shanahan, C. S.; Xu, X.; Doyle, M. P., *Org. Biomol. Chem.* **2014,** *12*, 5227-5234; (b) Saha, J.; Lorenc, C.; Surana, B.; Peczuh, M. W., *J. Org. Chem.* **2012,** *77*, 3846-3858; (c) Galloway, W. R. J. D.; Diáz-Gavilán, M.; Isidro-Llobet, A.; Spring, D. R., *Angew. Chem. Int. Ed.* **2009,** *48*, 1194-1196; (d) Rivera, D. G.; Vercillo, O. E.; Wessjohann, L. A., *Org. Biomol. Chem.* **2008,** *6*, 1787-1795.
3. (a) Sneddon, H., *Future Med. Chem.* **2014,** *6*, 1373-1376; (b) Liu, W.; Fu, Y.; Li, J.; Cai, C. N.; Lu, Z. M., *Chin. J. New Drugs* **2014,** *23*, 381-386; (c) Ager, D. J., *Synthesis* **2014,** *46*, A1-AI.
4. (a) Thevenet, N.; de la Sovera, V.; Vila, M. A.; Veiga, N.; Gonzalez, D.; Seoane, G.; Carrera, I., *Org. Lett.* **2015,** *17*, 684-687; (b) Bellomo, A.; Bertucci, A.; de la Sovera, V.; Carrau, G.; Raimondi, M.; Zacchino, S.; Stefani, H. A.; Gonzalez, D., *Lett. Drug Des. Discov.* **2014,** *11*, 67-75; (c) Carrau, G.; Drewes, C. C.; Shimada, A.; Bertucci, A.; Farsky, S.; Stefani, H. A.; Gonzalez, D., *Bioorg. Med. Chem.* **2013,** *21*, 4225-4232; (d) de La

Sovera, V.; Bellomo, A.; Gonzalez, D., *Tetrahedron Lett.* **2011,** *52*, 430-433; (e) de La Sovera, V.; Bellomo, A.; Pena, J. M.; Gonzalez, D.; Stefani, H. A., *Mol. Divers.* **2011,** *15*, 163-172; (f) Bellomo, A.; Bertucci, A.; Stefani, H. A.; Vazquez, A.; Gonzalez, D., *Tetrahedron: Asymmetry* **2009,** *20*, 2673-2676; (g) Bellomo, A.; Bonilla, J. B.; López-Prados, J.; Martín-Lomas, M.; Gonzalez, D., *Tetrahedron: Asymmetry* **2009,** *20*, 2061-2064; (h) Bellomo, A.; Camarano, S.; Rossini, C.; Gonzalez, D., *Carbohydr. Res.* **2009,** *344*, 44-51; (i) Bellomo, A.; Gonzalez, D.; Stefani, H. A., *J. Organomet. Chem.* **2008,** *693*, 1136-1142; (j) Bellomo, A.; Gonzalez, D., *Tetrahedron Lett.* **2007,** *48*, 3047-3051.

5. (a) Hudlicky, T.; Reed, J. W., *Synlett* **2009,** *2009*, 685-703; (b) Hudlicky, T.; Gonzalez, D.; Gibson, D. T., *Aldrichim. Acta* **1999,** *32*, 35-62; (c) Duchek, J.; Adams, D. R.; Hudlicky, T., *Chem. Rev.* **2011,** *111*, 4223-58.
6. Corne, V.; Botta, M. C.; Giordano, E. D.; Giri, G.; Llompart, D.; Biava, H.; Sarotti, A.; Mangione, M. I.; Mata, E. G.; Suárez, A. G.; Spanevello, R. A., *Pure Appl. Chem.* **2013,** *85*, 1683-1692.
7. (a) Sarotti, A. M.; Zanardi, M. M.; Spanevello, R. A.; Suarez, A. G., *Curr. Org. Synth.* **2012,** *9*, 439-459; (b) Sarotti, A. M.; Spanevello, R. A.; Suárez, A. G., *Tetrahedron Lett.* **2005,** *46*, 6987-6990; (c) Sarotti, A. M.; Joullié, M. M.; Spanevello, R. A.; Suárez, A. G., *Org. Lett.* **2006,** *8*, 5561-5564; (d) Sarotti, A. M.; Spanevello, R. A.; Suárez, A. G., *Org. Lett.* **2006,** *8*, 1487-1490; (e) Sarotti, A. M.; Fernández, I.; Spanevello, R. A.; Sierra, M. Á.; Suárez, A. G., *Org. Lett.* **2008,** *10*, 3389-3392; (f) Sarotti, A. M.; Spanevello, R. A.; Suárez, A. G., *Tetrahedron* **2009,** *65*, 3502-3508; (g) Zanardi, M. M.; Botta, M. C.; Suárez, A. G., *Tetrahedron Lett.* **2014,** *55*, 5832-5835; (h) Zurita, M. A.; Avila, A.; Spanevello, R. A.; Suárez, A. G.; Sarotti, A. M., *Carbohydr. Res.* **2015,** *402*, 67-70; (i) Zanardi, M. M.; Suárez, A. G., *Tetrahedron Lett.* **2015,** *56*, 3762-3765; (j) Gerosa, G. G.; Spanevello, R. A.; Suárez, A. G.; Sarotti, A. M., *J. Org. Chem.* **2015,** *80*, 7626-7634.
8. (a) Witczak, Z. J.; Tatsuta, K., *Carbohydrate Synthons in Natural Products Chemistry. Synthesis, Functionalization, and Applications.* . American

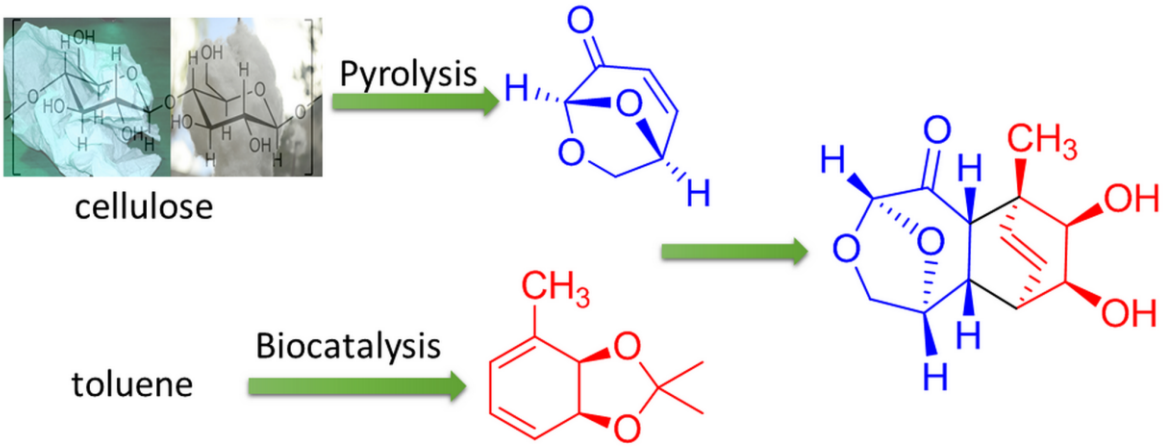
Chemical Society, Washington, DC, USA: 2003; (b) Witczak, Z. J., *Levoglucosenone and Levoglucosans Chemistry and Applications*. ATL Press: Mount Prospect, USA, : 1994.

9. Sarotti, A. M.; Spanevello, R. A.; Suarez, A. G., *Green Chem.* **2007,** *9*, 1137-1140.
10. Fringuelli, F.; Taticchi, A., *The Diels Alder Reaction. Selected Practical Methods* John Wiley & Sons, Inc: New York.: 2002.
11. Nicolaou, K. C. S., S. A.; Montagnon, T.; Vassilikogiannakis, G. , *Angew. Chem. Int. Ed.* **2002,** *41*, 1668-1698.
12. (a) Hudlicky, T.; Seoane, G.; Pettus, T., *J. Org. Chem.* **1989,** *54*, 4239-4243; (b) Hudlicky, T.; Olivo, H. F., *Tetrahedron Lett.* **1991,** *32*, 6077-6080; (c) Hudlicky, T.; Olivo, H. F.; McKibben, B., *J. Am. Chem. Soc.* **1994,** *116*, 5108-5115; (d) Gonzalez, D.; Martinot, T.; Hudlicky, T., *Tetrahedron Lett.* **1999,** *40*, 3077-3080; (e) Pazos, M.; Martínez, S.; Vila, M. A.; Rodríguez, P.; Veiga, N.; Seoane, G.; Carrera, I., *Tetrahedron: Asymmetry* **2015,** *26*, 1436-1447.
13. (a) Pittol, C. A.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Sik, V.; Williams, J. O., *J. Chem. Soc., Perkin Trans. 1* **1989**, 1160-1162; (b) Ley, S. V.; Redgrave, A. J.; Taylor, S. C.; Ahmed, S.; Ribbons, D. W., *Synlett* **1991,** *1991*, 741-742; (c) Hudlicky, T.; Boros, E. E.; Olivo, H. F.; Merola, J. S., *J. Org. Chem.* **1992,** *57*, 1026-1028; (d) Hudlicky, T.; Boros, C. H., *Tetrahedron Lett.* **1993,** *34*, 2557-2560; (e) Froese, J.; Hudlicky, J. R.; Hudlicky, T., *Org. Biomol. Chem.* **2014,** *12*, 7810-7819.
14. Banwell, M. G.; Austin, K. A. B.; Willis, A. C., *Tetrahedron* **2007,** *63*, 6388-6403.
15. CCDC number: CCDC-1472196.
16. CCDC number: CCDC-1472195.
17. (a) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A., *Tetrahedron* **2004,** *60*, 535-547; (b) Reekie, T. A.; Austin, K. A. B.; Banwell, M. G.; Willis, A. C., *Austr. J. Chem.* **2008,** *61*, 94-106.
18. (a) Houk, K. N.; Li, Y.; Evanseck, J. D., *Angew. Chem. Int. Ed.* **1992,** *31*, 682-708; (b) Liu, J.; Niwayama, S.; You, Y.; Houk, K. N., *J. Org. Chem.* **1998,** *63*,

1064-1073; (c) Jones, G. A.; Shephard, M. J.; Paddon-Row, M. N.; Beno, B. R.; Houk, K. N.; Redmond, K.; Carpenter, B. K., *J. Am. Chem. Soc.* **1999,** *121*, 4334-4339.

19. Butler, D. N.; Margetic, D.; O'Neill, P. J. C.; Warrener, R. N., *Synlett* **2000**, 98-100.

Graphical abstract



HIGHLIGHTS

- Chemoenzymatic construction of a complex homochiral tetracyclic structure in four steps.
- Enzymatic and biomass derived chiral synthons applied to the synthesis of a novel Natural Product-like molecule.
- Theoretically explained selectivity in the Diels-Alder cycloaddition of two enantiomerically pure partners.