

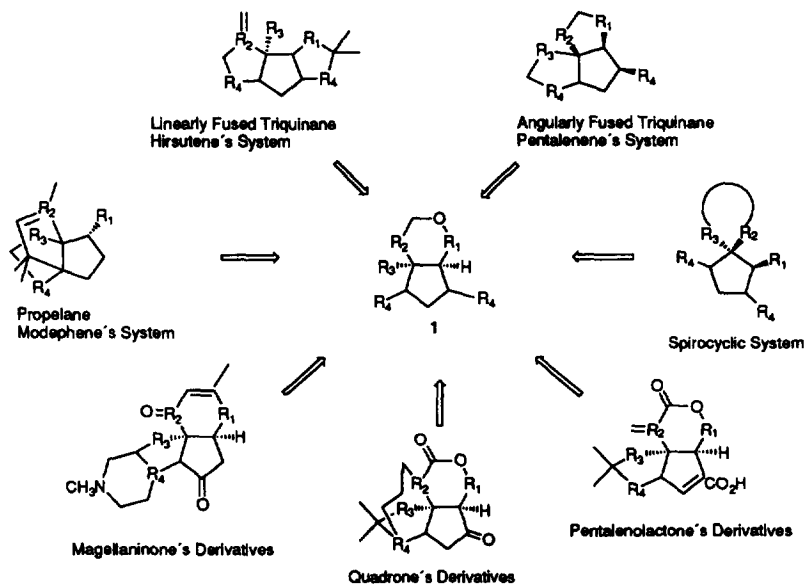
Efficient enantiospecific entry to a highly functionalized cyclopentane building block

Silvina C. Pellegrinet and Rolando A. Spanevello *

Instituto de Química Orgánica de Síntesis, CONICET–Universidad Nacional de Rosario, Facultad de Ciencias Químicas y Farmacéuticas, Casilla de Correo 991, 2000 Rosario, Argentina

Abstract: A simple and efficient route has been developed for the synthesis of a polyfunctionalized cyclopentane in enantiomerically pure form. D-Glucose is the source of chirality for this versatile building block and a highly diastereoselective Diels–Alder reaction with cyclopentadiene is the key step. © 1997 Elsevier Science Ltd

The simple observation of nature helps us to understand the essential role played by five membered carbocycles in natural products chemistry. The construction of a highly functionalized cyclopentane with a versatile substitution pattern like structure **1** could be envisioned as a direct approach to an ever increasing number of natural products possessing a wide variety of intricate carbocyclic skeletons in an optically pure form (Scheme 1).^{1–3}



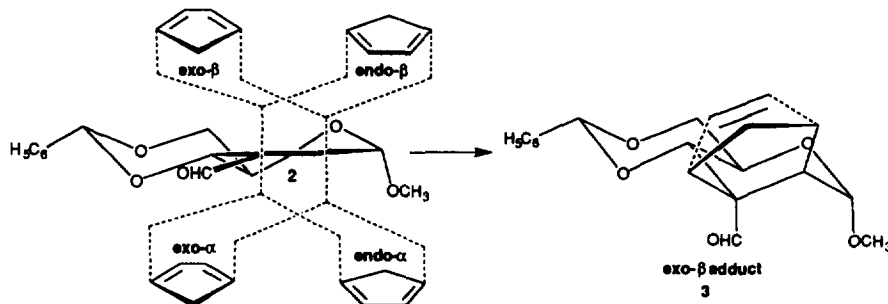
Our strategy is based on the use of a pyranoside ring as the initial scaffolding for the construction of a dienophile with an exocyclic electron withdrawing group. A Diels–Alder reaction with this template generates the required quaternary center in all these structures. We have already reported the synthesis of the α , β unsaturated aldehyde **2** from glucose,⁴ and found it is ideally suited for this purpose.

Even though several reports of the use of carbohydrate derived dienes and dienophiles in cycloaddition reactions have been published in recent years,^{5,6} to the best of our knowledge, there are only few examples of dienophiles bearing an exocyclic activating group.^{7,8} Furthermore, the degree of

* Corresponding author. Email: miquios@arcide.edu.ar

diastereoselectivity observed in many cases is not high enough to consider them as efficient processes and preclude their use in synthetic sequences.

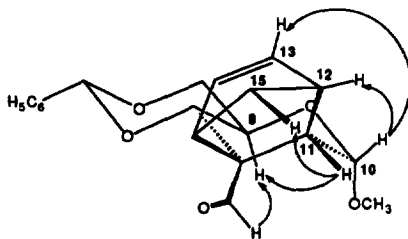
Herein we wish to report the highly diastereoselective outcome of the Diels–Alder reaction between the dienophile **2** and cyclopentadiene. In principle this cycloaddition process offers four possibilities, two different approaches from the α face and two others from the β face (Scheme 2).



Scheme 2.

The reaction of aldehyde **2** with freshly cracked cyclopentadiene in xylene at 80°C afforded cycloadduct **3**. This was the product arising from a β face approach in an *exo* manner. The same results were attained when the reaction was catalyzed by $\text{BF}_3\text{-OEt}_2$ in methylene chloride at -78°C or LiClO_4 in acetonitrile at room temperature.⁹ Shift reagents are also known to catalyze Diels–Alder reactions yielding, in some cases, different cycloadducts from those normally obtained with others Lewis acids, due to their hindered nature.¹⁰ When the reaction was catalyzed by YbFOD we obtained cycloadduct **3**. In all cases we were unable to detect any other diastereoisomer. The structure determination of compound **3** was based on spectroscopic evidences. The ^1H and ^{13}C NMR signals of **3** were unequivocally assigned by using homo and heteronuclear 2D NMR techniques.

The NOE observed between $\text{C}_{10}\text{-H}$ and $\text{C}_{13}\text{-H}$ and between $\text{C}_{12}\text{-H}$ and $\text{C}_{10}\text{-H}$ suggested the β approach. Further corroborations were obtained from irradiation of $\text{C}_{11}\text{-H}$ and the carbonyl proton which enhanced the $\text{C}_8\text{-H}$ signal (Scheme 3). The NOE observed between $\text{C}_{11}\text{-H}$ and one of the $\text{C}_{15}\text{-H}$ showed the *exo* character of the addition.



Scheme 3.

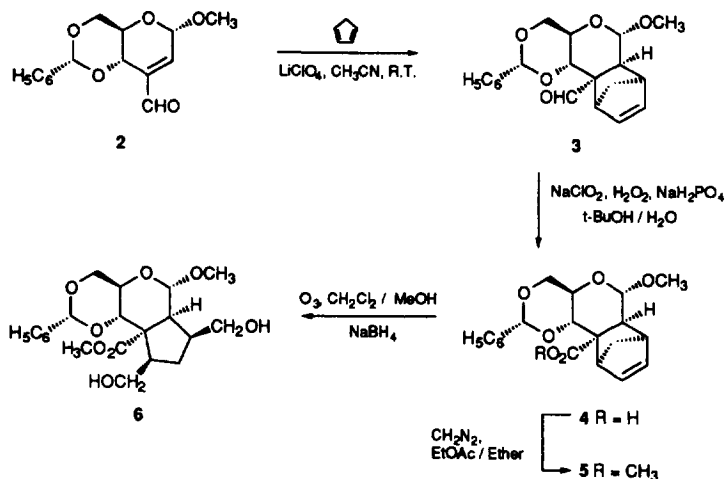
The bicyclic dienophile **2** is conformationally rigid, thus the diastereofacial selectivity could be rationalized in terms of the steric hindrance produced by the anomeric methoxy group on the α face. With regard to the *exo* attack, the explanation is not a simple one and will need further studies. However, based on literature precedents,¹¹ we could assume that the unfavorable interactions between $\text{C}_4\text{-H}$ and $\text{C}_6\text{-H}$ of the dienophile (sugar numbering) and the methylene group of the cyclopentadiene are responsible for this diastereoselection.

The aldehyde group in the dienophilic structure was by far the best substituent to accomplish the activation of the double bond in terms of reaction rate, yield and diastereoselectivity.¹²

The construction of the adduct **3** paves the way for the synthesis of the polysubstituted cyclopentane **6** through an oxidative cleavage of the olefin. At this stage it was necessary to change the oxidation

state of the carbonyl group in order to allow an adequate manipulation of the double bond. Oxidation of the aldehyde group and treatment of the acid **4** with diazomethane afforded the corresponding methyl ester **5**. For this oxidation process it was necessary to use sodium chlorite,¹³ since Jones reagent in acetone or silver oxide and sodium hydroxide in ethanol failed to accomplish this transformation.

Ozonolysis of the ester **5** and work up of the reaction with dimethyl sulfide furnished the dialdehyde in high yield but it proved to be very difficult to characterize due to its existence as a hydrate species. For that reason we decided to use a reductive work up with sodium borohydride which afforded the dihydroxyl compound **6** in 62% overall yield¹⁴ from **3** (Scheme 4).



Scheme 4.

The diol **6**¹⁵ offers multiple alternatives for further transformation into the different systems showed in Scheme 1.

Acknowledgements

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9. In a typical procedure, the dienophile **2** (3.750 g, 13.59 mmol) was dissolved in dry acetonitrile (136 mL) and stirred during 30 minutes with anhydrous LiClO₄ (7.2345 g, 67.95 mmol). Freshly cracked cyclopentadiene (9.125 mL, 135.90 mmol) was added under inert atmosphere at room temperature. The reaction was completed after 18 hs. The mixture was diluted with ethyl ether and washed with water. The organic layer was dried over Na₂SO₄, and concentrated under vacuum. Flash chromatography to remove the excess of bicyclopentadiene afforded compound **3** (4.0480 g, 11.84 mmol) in 85% yield.
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14. All compounds shown in Scheme 4 were fully characterized by spectroscopic techniques (¹H and ¹³C NMR, IR and MS). Compounds **3**, **5** and **6** gave satisfactory elemental analysis.
15. Recrystallization from isopropyl ether afforded compound **6** as white needles (m.p.=148–149°C).

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