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Enantiospecific Approach toward Pentalenolactone†

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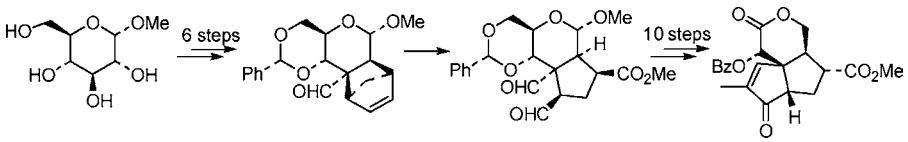
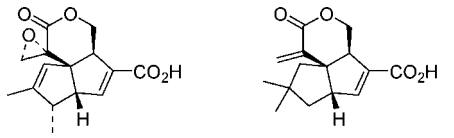
ABSTRACT



The enantiospecific assembly of the pentalenolactones' carbon skeleton was achieved in 17 steps and 16% overall yield from methyl α-D-glucopyranoside. The synthetic strategy relies on two highly efficient key steps: an *exo*-diastereoselective Diels–Alder reaction and a nonsymmetric ozonolysis.

The pentalenolactone-type sesquiterpenoids are a growing family of structurally unprecedented natural products produced by prokaryotic organisms that share a unique tricyclic ring skeleton. Pentalenolactone (**1**; Figure 1) was the first



1: Pentalenolactone 2: Pentalenolactone E

Figure 1. Members of the pentalenolactone family.

metabolite in this class to be isolated. Its structure and absolute configuration were established in 1970, but in recent times, several new cometabolites have been isolated.[1] Cane et al. and others have also recently reported detailed studies on the biosynthesis of this type of compound.[2]

Pentalenolactone **1** has broad spectrum activity as an antibiotic against gram-positive and gram-negative strains of bacteria and pathogenic and saprophytic fungi. It has proven antitumor properties and is also a potent and specific antiviral agent; it inhibits the replication of DNA viruses, including HSV-1 and HSV-2, the causal agent of herpes simplex.[3] Of special importance, however, is the glycolytic blocking action of pentalenolactone in both prokaryotic and eukaryotic species by the selective inhibition of glyceraldehyde-3-phosphate dehydrogenase. This enzyme catalyzes the reversible NAD^+-dependent oxidative phosphorylation of glyceraldehyde-3-phosphate to 1,3-diphosphoglycerate.

The striking biological properties of this compound have aroused considerable interest in different research areas. Special efforts have been devoted to study the inhibitory effects of **1** on glyceraldehyde-3-phosphate dehydrogenase in *Trypanosome brucei*.[4] This haemoflagellate protozoan, the causative agent of African sleeping sickness, has an unusual compartmentalization of its glycolytic pathway. The selective inhibition of this enzyme has shown to block its glycolytic process, thus provoking an immediate depletion of ATP from

† Dedicated to Professor K. C. Nicolaou on the occasion of his 60th aniversary.

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the cell, followed by rapid disappearance of the parasite from the host's bloodstream. This effect is due to the fact that bloodstream trypomastigotes of the *Trypanosome brucei* group depend exclusively on glycolysis for their energy metabolism.[5]

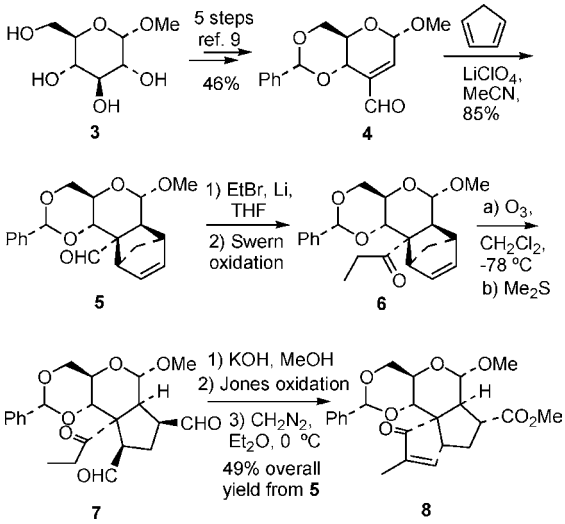
From the synthetic point of view, there has been sustained interest in the chemistry of these natural products over the past few decades. Analysis of their molecular structures show a highly compacted carbon skeleton, with an angularly fused tricycle pentanoid lactone and different oxidation states in each of the rings, which combine to present a real synthetic challenge. Since the first total synthesis of pentalenolactone was published in 1978, there have been many reports (more than 20) toward the synthesis of this family of compounds.[6]

Notwithstanding this, only two research groups have addressed the issue of optical purity in the synthesis of (−)-pentalenolactone E methyl ester (**2**) by an enzymatic resolution of an advanced synthetic intermediate.[7,8] However, to the best of our knowledge, no general enantiospecific approach toward the synthesis of this quaternary carbon-centered polycyclic structure has yet been reported. In light of these considerations, we were prompted to devise a simple means for building the pentalenolactone quinane skeleton in an enantiospecific form.

Our asymmetric strategy relies on the use of D-glucose as the source of chirality. In a simple and straightforward synthetic sequence, we have converted the methyl-α-D-glucopyranoside (**3**) into the cyclic α,β-unsaturated aldehyde (**4**).[9]

Treatment of aldehyde **4** with cyclopentadiene afforded the cycloadduct **5** as the only detectable product in 85% yield (Scheme 1).[10] In principle, the Diels−Alder reaction offers

Scheme 1. Synthesis of the Bicyclic [3.3.0] Octene **8**



four possibilities, two different approaches from the α-face and two from the β-direction, but the outcome of this reaction is highly diastereoselective and proceeds mainly through the β-face of the dienophile in an *exo* manner.[11]

The bicyclic dienophile **4** is conformationally rigid, and we expected that the steric hindrance produced by the anomeric methoxy group on the α-face would preclude any attack from this face. We relied on this reaction selectivity to establish the configuration of the quaternary carbon, pivotal to the angular tricyclic junction.

Even though the initially unexpected *exo*-isomer has the olefin bridge with the opposite configuration (it is *trans* with respect to the aldehyde group), we found it was equally suitable to achieve our goal.

Barbier-type nucleophilic addition of ethyllithium, followed by a Swern oxidation of the resulting mixture of epimeric alcohols, yielded ketone **6**. Ozonolysis of the double bond set the stage for assembly of the core bicyclic [3.3.0] octene framework. Intramolecular aldol condensation, under basic conditions, of the tricarbonyl intermediate **7** led to the carbon stereocenter attached to the aldehyde group to become epimerized and allowed an efficient ring closure. Jones oxidation of the remaining aldehyde group and esterification with diazomethane afforded the methyl ester (**8**) in 49% overall yield from **5**.[12] Unfortunately, although compound **8** embodied the carbon skeleton associated with this family of sesquiterpenes, we failed in all our attempts to form the required double bond after a conjugate additon of methyllithium to the α,β-unsaturated ketone, to make an S_N2'

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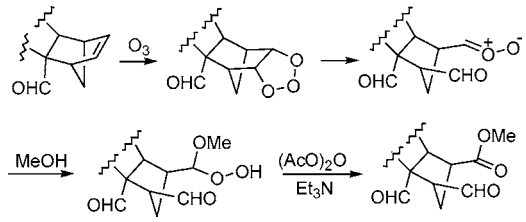
substitution on the corresponding allylic alcohol derivatives, or to make a 1,3-carbonyl transposition. We reached a dead end that we attributed to the hindered nature of the carbonyl position, which forced us to redesign the synthetic strategy.

As an alternative approach, we decided to use the scantily explored unsymmetrical ozonolysis first reported by Schreiber et al.[13] in 1982.

These experimental conditions convert cycloalkenes into terminally differentiated products. Even though we did not know a priori what kind of cleavage pattern we would obtain, to our delight, the reaction was a great success.

The key step in this reaction is the regioselective cycloreversion or fragmentation process of the primary ozonide providing a transient carbonyl oxide and a stable carbonyl group. The carbonyl oxide is trapped with methanol, a participating solvent, to give a methoxy hydroperoxide that is subsequently dehydrated upon treatment with acetic anhydride and triethylamine in a one pot reaction (Scheme 2).

Scheme 2. Ozonolysis Pathway



Starting again from the cycloadduct **5**, unsymmetrical ozonolysis of its norbornene system in dichloromethane−methanol and sodium bicarbonate unveiled a new substitution pattern for the cyclopentane moiety of **9** in almost quantitative yield (Scheme 3).

The penta-substituted cyclopentane bears two aldehyde groups (one from the original starting material attached at the quaternary center and the newly formed one) and a methyl ester. This highly nonsymmetric process is evidently controlled by substituents that are at least at a two-carbon distance from the double bond.

As far as we know, this is the first example of a completely regioselective cleavage of a primary ozonide controlled by remote substituents in a complex molecular system that has furnished an aldehyde group on one terminus and a methyl ester on the other.[14]

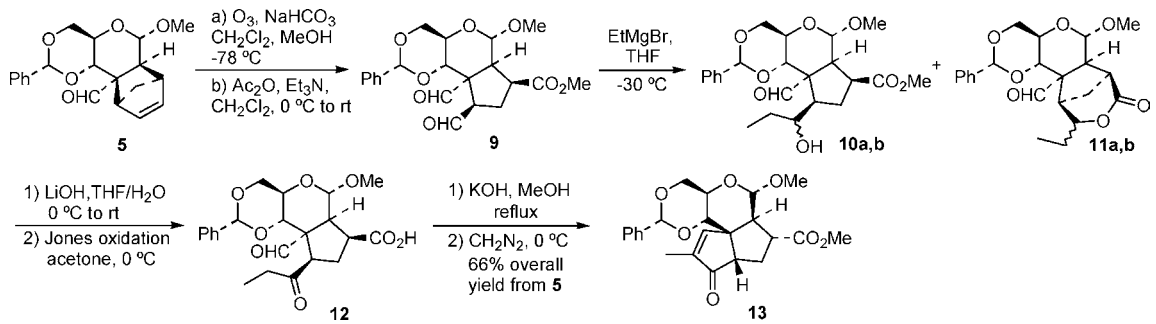
Given the encumbered nature and lower reactivity of the carbonyl group attached at the quaternary center, we were able to manipulate each group regioselectively. Thus, it was possible to carry out a nucleophilic addition on the less-hindered aldehyde group of **9** without affecting the other one or the methyl ester. Indeed, Grignard addition of the alkyl side chain was achieved in a completely regioselective manner. However, the reaction furnished a mixture of two pairs of epimeric products: the desired alcohols **10a**,**b** and the tetracyclic lactones **11a**,**b**. The complexity of the mixture prompted us to use the crude mixture directly for the next steps, which were alkaline hydrolysis and Jones oxidation. Again, we took advantage of the steric hindrance surrounding the aldehyde to oxidize the secondary alcohol without affecting the free carbonyl group. Success was verified by the ^{1}H NMR spectrum of the crude reaction product, which revealed that the ethyl ketone (**12**) was the only reaction product formed. Compound **12** bears an aldehyde and an ethyl ketone adequately located to undergo an intramolecular aldol reaction.

The aldol reaction, under basic conditions, produced the epimerization of the carboxylic and ketone groups α-carbons, paving the way for an efficient cyclization. Finally, esterification of the carboxylic acid and purification of the resulting material afforded the methyl ester **13** in 66% overall yield from cycloadduct **5** (Scheme 3). This new route not only represents a formal 1,3-carbonyl transposition of the α,β-unsaturated ketone moiety present in **8**, but also affords a substantially increased overall yield. In this way, we managed to introduce a double bond in the right position, circumventing the steric problems of the neopentylic carbonyl group encountered in compound **8**. Enone **13** possesses functionality that may allow further transformation into any of the natural products of this class.

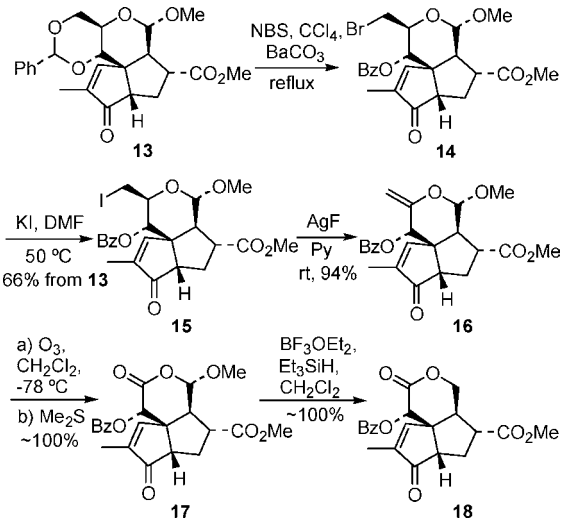
At this point, we decided to pursue the construction of the lactone ring. This route involved the regioselective ring opening of the benzylidene acetal following Hanessian's procedure,[15] which led to the formation of the bromide **14** (Scheme 4).

Subsequently, an efficient interchange of halogen was carried out to furnish the iodide **15** in 66% yield (two steps)

Scheme 3. Synthesis of the Cyclic Enone **13**



Scheme 4. Synthesis of the Lactone **18**



which, afterward, was treated with pyridine and silver fluoride[16] to obtain the enol ether (**16**) in 94% yield. It is worth mentioning that the dehydrohalogenation reaction of bromide **14** under the same experimental conditions gave the enol ether in very poor yield. This is the reason we chose the two-step sequence previously described.

Chemoselective ozonolysis of the exocyclic enolate was possible due to the difference in electronic density between this double bond and the endocyclic one, plus possible steric factors that make this transformation very efficient.

The reductive cleavage of the glycoside bond was not a trivial step. After the failure of several strategies aimed at obtaining the product with reasonable yields, we finally achieved our goal by treating the alkoxy-lactone **17** with boron trifluoroetherate and triethylsilane.[17] This procedure cleanly afforded the lactone moiety (**18**) in essentially quantitative yield.

In conclusion, we have reported the enantiospecific construction of the core bicyclic [3.3.0] octene framework **18** of pentalenolactone in 17 steps and 16% overall yield. Our strategy relies on two highly efficient key steps: the *exo*-diastereoselective Diels−Alder reaction and the nonsymmetric ozonolysis. Product (**18**) bears all the functionality necessary to achieve the synthesis of all the members of this family of natural products

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Supporting Information Available: General experimental procedure and NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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