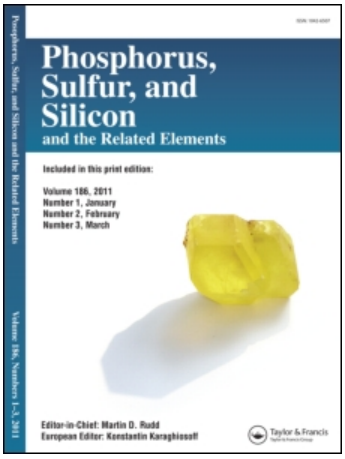

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Phosphonate-Mediated Synthesis of Biologically Active Cyclopentanones and Cyclopentenones

Marian Mikołajczyk[a]
[a] Center of Molecular and Macromolecular Studies, Polish Academy of Sciences, Sienkiewicza 112, Poland

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PHOSPHONATE-MEDIATED SYNTHESIS OF BIOLOGICALLY ACTIVE CYCLOPENTANONES AND CYCLOPENTENONES

Marian Mikołajczyk
Center of Molecular and Macromolecular Studies, Polish Academy of Sciences, 90-363 Łódź, Sienkiewicza 112, Poland

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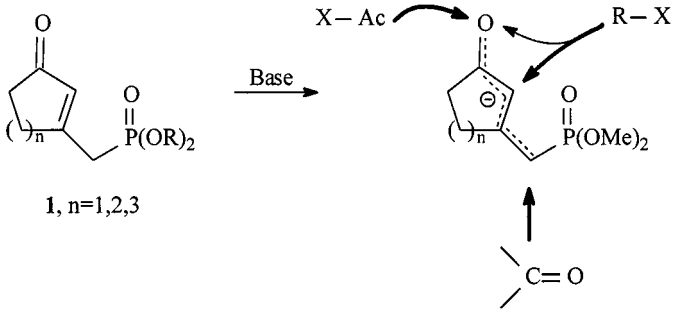
The synthesis and reactivity of 3-(phosphorylmethyl)cyclopent-2-enones as well as a complete desymmetrization of meso*-tartaric acid are discussed as a platform for developing the synthesis of racemic rosaprostol and enantiomeric forms of prostaglandin B_1 methyl ester, isoterrein, and neplanocin A.*

Keywords: Desymmetrization; Horner-Wittig reaction; isoterrein; *meso*-tartaric acid; neplanocin; phosphonates; prostaglandin B_1; rosaprostol.

INTRODUCTION

Organophosphorus compounds occupy a unique role in the arsenal of reagents that are useful in organic synthesis. In the course of our studies on the synthesis of cyclopentanoid antibiotics (methylenomycin A and B, sarkomycin), we demonstrated that the use of various phosphonate reagents (α-methylsulfenylphosphonates, β-keto, and γ-ketophosphonates) offers several important advantages.[1] Our further studies directed toward the synthesis of functionalized cyclopentenones resulted in the development of a general synthesis of 3-(phosphorylmethyl)cycloalk-2-enones **1**. The reactivity of the anion derived from **1** (see Scheme 1) opened a new way for the synthesis of variously substituted bioactive cyclopentanones and cyclopentenones.[2]

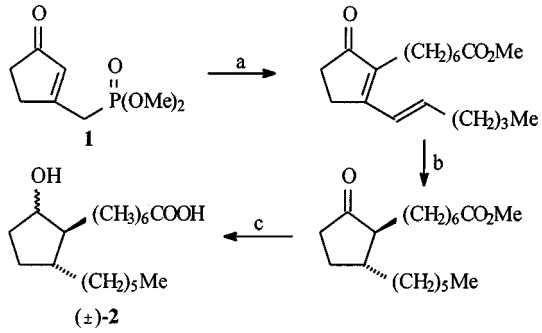
Address correspondence to M. Mikołajczyk, Center of Molecular and Macromolecular Studies, Polish Academy of Sciences, 90-362 Łódź, Sienkiewicza 112, Poland. E-mail: marmikol@bilbo.cbmm.lodz.pl



SCHEME 1

SYNTHESIS OF RACEMIC ROSAPROSTOL

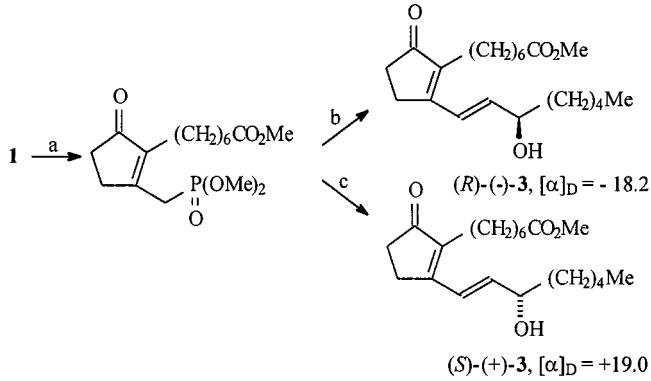
Rosaprostol **2**, an antiulcer drug, was prepared in five steps and in 36% overall yield starting from **1**. The regioselective alkylation of **1** at the α-carbon atom with methyl 7-iodoheptanoate, and subsequent Horner-Wittig reaction with pentanal, constituted the key steps in this total synthesis as showed in Scheme 2.[3]



SCHEME 2 (a) $I(CH_2)_6CO_2Me$, NaH/DMSO; (b) H_2/PtO_2, AcOH; (c) H_2O/NaOH, $NaBH_4$.

SYNTHESIS OF (+)- AND (−)-PROSTAGLANDIN B_1

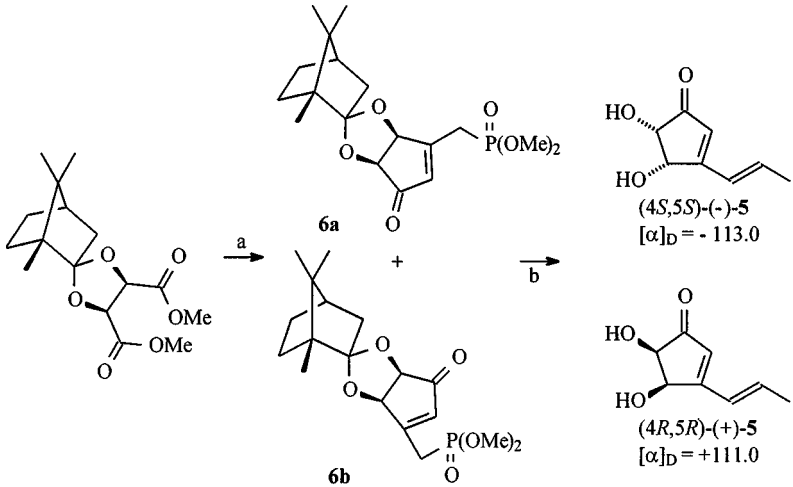
The cyclopentenone **1** was converted in two steps into enantiomeric forms of the title compound **3** (Scheme 3). The first involved regioselective alkylation at C(2) with methyl 7-iodoheptanoate. The use of (*R*)- and (*S*)-2-(*tert*-butyldimethylsilyloxy)heptanal **4** for the Horner-Wittig reaction gave, after deprotection of the hydroxy group, the enantiopure forms of **3** in 28% overall yield.[4]



SCHEME 3 (a) $I(CH_2)_6CO_2Me$, NaH/DMSO; (b) (*R*)-(+)-**4**, DBU/$LiClO_4$; Bu_4NF; (c) (*S*)-(-)-**4** and as in (b).

SYNTHESIS OF (+)- AND (−)-ISOTERREIN

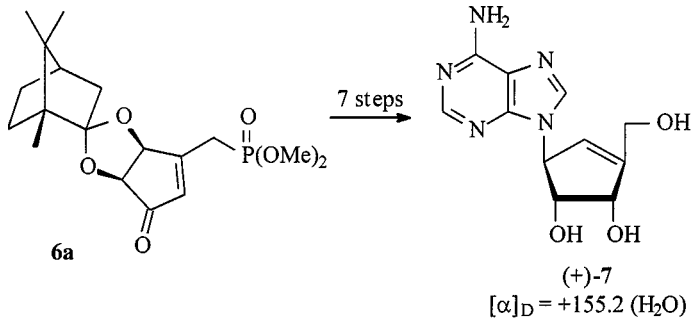
A crucial step in the synthesis of both enantiomers of **5** was complete desymmetrization of *meso*-tartaric acid, which upon treatment with (+)- camphor yielded the corresponding ketal as a single diastereomer. The latter was converted into separable mixture of protected 3-phosphorylmethylcyclopentenones **6**, which in turn, upon Horner-Wittig reaction, will acetaldehyde and acidic hydrolysis afforded enantiomeric isoterreins **5** (see Scheme 4).[5]



SCHEME 4 (a) $(MeO)_2P(O)CH_2Li$; (b) separation, BuLi, MeCHO; $H_3O^{\oplus}$/dioxane.

SYNTHESIS OF (+)-NEPLANOCIN A

The diastereomeric camphor protected 3-phosphorylmethylcyclo-pentenone **6a** was used as substrate in the total synthesis of unnatural (+)-neplanocin A **7**, a member of the carbocyclic nucleoside family. This synthesis (Scheme 5) involved seven steps and afforded the desired product in 12.5% overall yield.[6]



SCHEME 5

CONCLUSIONS

As we have shown, 3-phosphorylmethylcyclopentenones are very useful reagents in the synthesis of biologically active products. Our syntheses compare favorably in terms of the use of simple reagents and transformations with the majority of the previously reported syntheses. Without a doubt, this new strategy for the synthesis of functionalized cyclpentanones and cyclopentenones will have more applications in the synthesis in forthcoming years.

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