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Enantioselective synthesis of the carbocyclic moiety of (−)-carbovir

Emmanuel Roulland, Claude Monneret and Jean-Claude Florent*

UMR 176 CNRS-Institut Curie, Section Recherche, 26 rue d'Ulm, 75248 Paris Cedex 05, France

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Abstract—Enantioselective construction of the protected carbocycle moiety of the anti-HIV drug carbovir was achieved in 11 steps from (*S*)-(−)-ethyl lactate. The two key steps are a Claisen [3+3] sigmatropic rearrangement of (3*S*,4*E*)-3-(4-methoxy-phenoxymethyl)-hex-4-enoic acid dimethylamide and next, a ruthenium-catalysed ring closure metathesis leading to (1*S*,4*S*)-4-(4-methoxy-phenoxymethyl)-cyclopent-2-enol. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Optically pure 4-(*tert*-butyl-dimethyl-silanyloxymethyl)-cyclopent-2-enol **1**[1] is of great interest as a building block used for the introduction of the pseudo-ribose moiety present in the structure of the anti-HIV drug (−)-carbovir **3a** and abacavir **3b** (Fig. 1).[2] This carbocycle, with its correct chirality, will mimic the ribose moiety of natural nucleosides.

The primary hydroxyl moiety is indeed phosphorylated by the cellular nucleoside kinases before the viral reverse transcriptase incorporates the resulting pseudo-nucleoside into the growing nucleic acid chain, thus leading to the termination of the DNA elongation. In continuation of previous studies on the synthesis of asymmetric polysubstituted cyclopentenes, we wish to report an enantioselective preparation of the building block **2** closely related to **1**.[3] In order to obtain cyclopentenol **A** (Scheme 1), we chose an extension of our strategy[4] based on a ruthenium-catalysed ring closure metathesis (RCM) and [3+3] sigmatropic rearrangement. Thanks to this strategy, cyclopentenol **A** could be obtained by RCM of the 1,5-diene **B**, itself resulting from amide **C**. This could be prepared from the asymmetric alcohol **D** through a Claisen [3+3] sigmatropic rearrangement, (*S*)-ethyl lactate being used as the source of chirality.

2. Results and discussion

Our synthesis started from the readily available (*S*)-(−)-ethyl lactate **4** (Scheme 2). First, the hydroxyl function was protected with a *tert*-butyldiphenylsilyl group to give compound **5** quantitatively, then the ester moiety was reduced using di-*iso*-butylaluminium hydride, affording the corresponding aldehyde which was directly used in the next step without further purification.

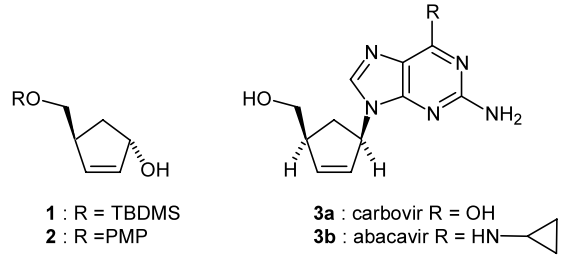
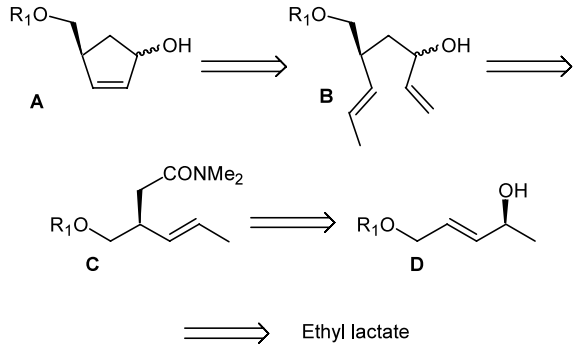


Figure 1.



Scheme 1.

* Corresponding author. Tel.: +33-(0)1-42-34-66-58; fax: +33-(0)1-42-34-66-31; e-mail: jean-claude.florent@curie.fr

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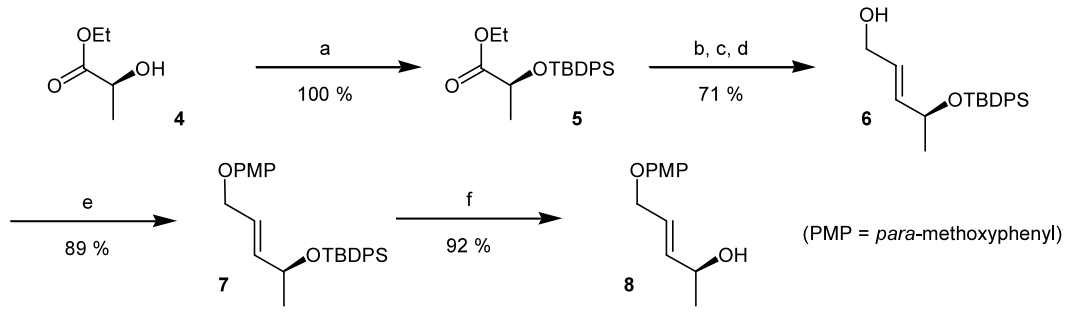
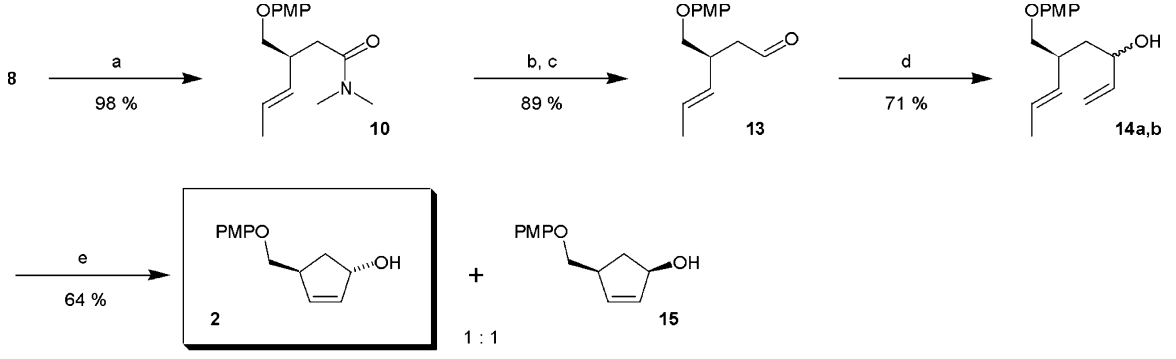


Scheme 2. *Reagents and conditions*: (a) *tert*-$BuPh_2SiCl$, imidazole, CH_2Cl_2, rt; (b) *iso*-Bu_2AlH, CH_2Cl_2, −78°C; (c) $Ph_3P{=}CHCO_2Et$, PhMe, 80°C. (d) *iso*-Bu_2AlH, THF, −78°C to 0°C; (e) DEAD, PPh_3, 4-MeOPhOH, THF, rt; (f) TBAF, THF, rt.

The salt-free Horner–Emmons reaction with (carboethoxymethylene)triphenylphosphorane exclusively led to an α,β-unsaturated ethyl ester of *E* configuration. This ester was then reduced to an alcohol **6** using 2 equiv. of di-*iso*-butylaluminium hydride (71% from **5**). A protection of the primary hydroxyl function was achieved via a Mitsunobu reaction[5] with 4-methoxyphenol, affording 4-methoxyphenyl ether (PMP) ether **7**. Deprotection of the secondary alcohol function of compound **7**, carried out using tetrabutylammonium fluoride, gave optically pure compound **8** in 58% yield from ethyl lactate. A Claisen [3+3] sigmatropic rearrangement reaction was then undertaken using dimethylacetamide dimethylacetal in refluxing decahydronaphthalene,[6] which readily rearranged, exclusively leading to the dimethylamide **10** via the vinyl ether intermediate **9** (Scheme 3). As depicted in Figure 2, the [3+3] sigmatropic rearrangement of intermediate **9** took place via the transition state **A** of lower energy. For this reason, the reaction led to exclusive formation of the *S* isomer **10** featuring an *E* double bond. The (*R*,*Z* isomer **11** was not detected by ^1H NMR). The actual optical purity of the rearranged product **10** was easily verified at the last step of our synthesis. The *N*,*N*-dimethylamide compound **10** was then converted into the aldehyde **13** in two steps: (i) treatment of **10** with 3 equiv. of lithium triethylborohydride[6] led to alcohol **12**, (ii) subsequent Swern oxidation[7] gave the aldehyde **13** in 89% overall yield. The second ethylenic function was then introduced via a reaction with vinyllithium, affording the 1,6-diene as an equimolar mixture of the two possible diastereoisomers **14a** and **14b**. The RCM reaction of 1,6-dienes **14a**,**b** was then achieved using Grubbs' catalyst,[8] leading to a mixture of two cyclopentenols: the expected compound **2** and his diastereoisomer **15**.



Scheme 3. *Reagents and conditions*: (a) $Me_2N(MeO)_2CCH_3$, decalin, reflux; (b) $LiEt_3BH$, THF, −78°C to rt; (c) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C, then NEt_3; (d) $BrHC{=}CH_2$, *tert*-BuLi, −78°C, THF; (e) $Cl_2(Cy_3P)_2Ru{=}Bn$, CH_2Cl_2, rt.

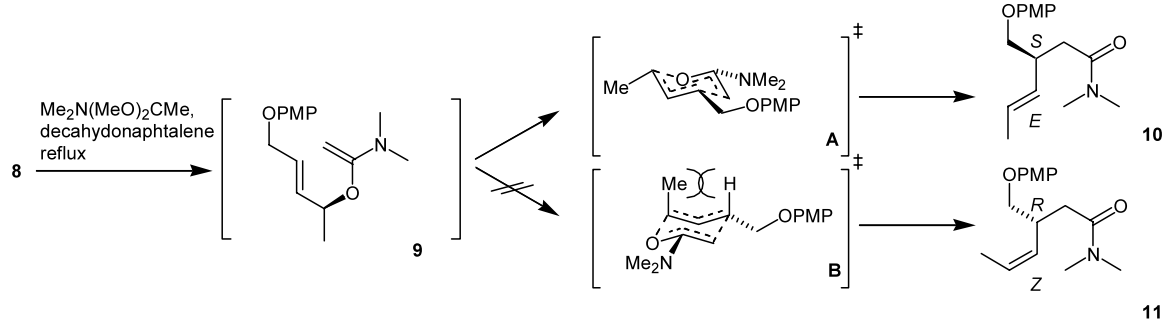


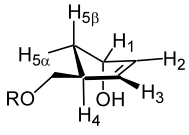
Figure 2. Transition state in the Claisen [3+3] sigmatropic rearrangement reaction.

Table 1. Chemical shifts of *trans* cyclopentenols **1** and **2** (ppm)

Entry		$H_{5\beta}$	$H_{5\alpha}$	H_1	H_2	H_3	H_4
1	**2** $\delta =$	1.95	2.07	4.96	6.05	5.96	3.35
2	**1** $\delta =$	1.77	1.91	4.78–4.92	5.94	5.85	2.85–3.10

Table 2. Observed and computed coupling constants for cyclopentenols **2** and **1**

Entry		H_1–$H_{5\alpha}$	H_4–$H_{5\beta}$	H_4–$H_{5\alpha}$	H_1–$H_{5\beta}$
1	Coupling constants for **2**	7.1 Hz	7.8 Hz	4.9 Hz	3.2 Hz
2	Calculated torsion angles for **2**	−28°	+155°	+35°	+91°
3	Estimated coupling constants for **2**	7 Hz	7.5 Hz	5.5 Hz	0 Hz
4	Coupling constants for **1**	7.3 Hz	7.8 Hz	4.6 Hz	3.3 Hz



1 : R = TBDMS
2 : R = OPhOMe

A very fast RCM reaction (less than 1 h) was observed, consistent with the reported[9] reaction speed for 1,6-dien-3-ol. Separation of **2** and **15** was easily performed by flash chromatography.

The ^1H NMR study of the compounds **2** and **15** allowed us to assign their absolute stereochemistries. The homoallylic protons $H_{5\alpha}$ and $H_{5\beta}$ provided most of the information. In Table 1, summarised are the ^1H NMR signals of compound **2**. These values can be compared with the reported signals of the related compound **1**.[1b] It is a general observation that chemical shifts of the geminal H_5-protons of *cis*-1,4-disubstituted-cyclopentenes present large differences, often in the range of 1 ppm.[10] On the other hand, this difference does not usually exceed 0.3 ppm for the *trans* isomers. As seen in Table 1, the differences between $H_{5\alpha}$ and $H_{5\beta}$ signals for products **2** and **1** are smaller than 0.3 ppm. A further computer-based modelisation, using the random search function (SYBYL 6.5/Tripos force field), gave the conformer of lowest energy for compound **2**. From this, a calculation of the coupling constants could be done and gave values similar to the observed one (Table 2).

It is well known that Claisen rearrangements occur with complete transfer of the chirality of the alcohol function as depicted in Figure 2. However, a confirmation of this was achieved in our case by performing ^1H NMR experiments on cyclopentenol **2** in the presence of chiral europium salt ($Eu(hfc)_3$). Thus, since no ^1H signal split was observed, the high enantiomeric excess of **2** was assessed.

3. Conclusion

The preparation of carbovir **3** reported by Asami et al.[1b] should be compatible with the protective group, since it can be easily removed with cerium ammonium nitrate or with smooth anodic oxidation.[5b,c,d] Our strategy, based on a Claisen rearrangement followed by a metathesis-based ring closure, provides an original entry in the RCM-based preparation of five-membered carbocycles and thus completes other preparations of polysubstituted cycles previously reported.[11] It is also noteworthy that other carbocyclic nucleosides have recently been constructed using metathesis strategy.[2g]

Acknowledgements

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3. Analytical data for compound **2**. $[\alpha]_D^{25}$ −69 (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) 3596, 2917 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.95 (ddd, 1H), 2.07 (ddd, 1H), 3.35 (m, 1H), 3.77 (s, 3H), 3.82 (m, 2H), 4.96 (brs, 1H), 5.96 (m, 1H),

6.05 (m, 1H), 6.83 (s, 4H); DCI-HRMS m/z calcd for MH^+, $C_{13}H_{16}O_3$: 220.1099. Found: 220.1098.

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