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Authors	Bemba Sidi Mohamed, Suzanne Peyrottes, Jean-Pierre Uttaro and Christophe MATHE
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ORCID® iDs	Christophe MATHE - https://orcid.org/0000-0003-3114-9361

Straightforward chemical desymmetrisation of cis-(±)-4-*O*-protected-cyclopent-2-enol using resolving agents on column chromatography

Bemba Sidi Mohamed, Suzanne Peyrottes, Jean-Pierre Uttaro, Christophe Mathé*

Institut des Biomolécules Max Mousseron (IBMM), UMR 5247, Université de Montpellier, CNRS, ENSCM, cc 1705, Site Triolet, Place Eugène Bataillon
34095 Montpellier cedex 5, France.

Email: christophe.mathe@umontpellier.fr

Abstract

A simple and efficient procedure for the separation of cis-(+)- and cis-(–)-4-*O*-protected-cyclopent-2-enol, from the corresponding racemic mixture as starting material and using resolving agents, is described. The separation of diasteroisomers was accomplished by flash silica gel column chromatography. The enantiomers cis-(+)- and cis-(–)- of 4-*O*-protected-cyclopent-2-enol were obtained, in enantiomeric pure form, after elimination of the resolving agents.

Keywords

cis-4-*O*-TBS-cyclopent-2-enol • chiral building blocks • resolving agents • chemical desymmetrization • (*R*)-(+)-*O*-mandelic acid

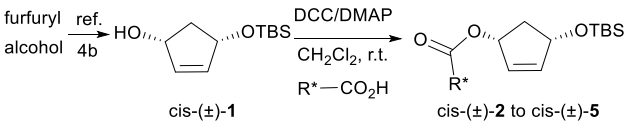
Introduction

The preparation of optically active cis-(+)- and cis-(–)-4-*O*-protected-cyclopent-2-enol is raising a great interest because of their potential use as chiral building blocks. Many examples in the literature report their use as a chiral precursor for the enantioselective synthesis of carbocyclic nucleosides [1], total synthesis of natural products [2] and prostaglandin derivatives [3]. Previously reported preparations of enantiomeric pure cis-2-cyclopentene-1,4-diol employ enzymatic resolutions of 4-*O*-protected derivatives [4] or chemical desymmetrisation of meso-cyclopentenoids using a palladium complex of the Trost ligand [5]. However, these procedures are not necessarily user-friendly. They require the use of biocatalysts or catalysts that can be expensive, time consuming and difficult to implement on a large scale in order to obtain substantial amounts of chiral building blocks. In order to quickly and easily access these chiral building blocks, we present herein a new and simple procedure for chromatographic separation of cis-(+)- and cis-(–)-4-*O*-protected-cyclopent-2-enol using resolving agents and the corresponding racemic mixture as starting material.

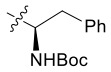
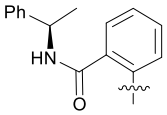
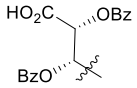
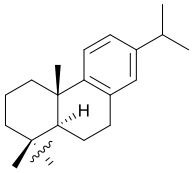
Results and Discussion

As starting material, we selected cis-(±)-4-*O*-tert-Butyldimethylsilyl-cyclopent-2-enol 1 which was readily prepared in three steps and in large scale (≈ 10 g) from commercially available bio-sourced furfuryl alcohol following reported procedures [4b]. Among the common resolving agents [6], we considered the following ones: (*R*)-(+)-*O*-mandelic acid, (–)-N-Boc-D-phenylalanine, (*R*)-(+)-N-(1-phenylethyl)phthalamic acid, (–)-dibenzoyl-L-tartaric acid and (+)-dehydroabietic acid. DCC/DMAP mediated coupling (Steglich esterification) [7] was chosen as convenient method for the introduction of the resolving agents. The results are outlined in Table 1.

Table 1: Coupling reaction with resolving agents



cis-(±)-**1** cis-(±)-**2** to cis-(±)-**5**

Compounds	R*	Time	Yield[a] (%)
cis-(±)-**2**		2h	93
cis-(±)-**3**		3h	96
cis-(±)-**4**		6d	41
cis-(±)-**5**		6d	63
I		10d	No reaction

[a] Yield of diastereoisomeric mixture after simple purification by column chromatography in isocratic conditions

The coupling reaction with cis-(±)-4-*O*-TBS-cyclopent-2-enol was performed in presence of DCC (1.5 eq.) and DMAP (0.1 eq.) in anhydrous dichloromethane under argon atmosphere and the different resolving agents (1.5 eq.) considered in the study. Under these conditions, the use of (*R*)-(+)-*O*-mandelic acid and (–)-N-Boc-D-phenylalanine led to total disappearance of the starting material in a short reaction time to afford, after preliminary purification on silica gel column, the corresponding adducts (±)-2 and (±)-3 in 93% and 96%, respectively. However, when using (*R*)-(+)-N-(1-phenylethyl)phthalamic acid and (–)-dibenzoyl-L-tartaric acid a longer reaction time was required and lower yields were obtained for derivatives (±)-4 and (±)-5. No coupling reaction occurred with (+)-dehydroabietic acid. Based on these results, adducts (±)-2 and (±)-3 were selected for further study to determine the best eluent

system giving a suitable separation of the corresponding diastereoisomers on Thin Layer Chromatography (TLC). In the case of (±)-2, the best results on TLC were obtained with petroleum ether/dichloromethane (PE/DCM) (1/1: v/v). For adduct (±)-3, none eluting system tested allowed separation on TLC. In order to optimize the separation of the diastereoisomers of (±)-2, we envisaged the use of flash chromatography purification system with PE/DCM as eluent by varying various parameters such as the amount of compound (±)-2, the mass of the silica as well as its granulometry (see General protocols in the supporting information). These results are summarized in Table 2.

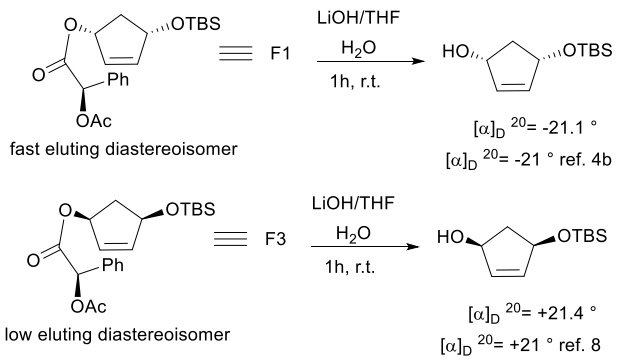
Table 2: Optimization of silica gel chromatographic separation conditions

Entry	**Conditions**	**(±)-2 mass**	**Silica mass**	**granulometry**	**Mass of fractions mg** (% separation in weight)		
					F1	**F2**	**F3**
1	Flash purification	500 mg	40 g	40 µm	220 (44%)	185 (37%)	95 (19%)
2	Flash purification	500 mg	40 g	15 µm	190 (38%)	110 (22%)	200 (40%)
3	Flash purification	500 mg	80 g	40 µm	245 (49%)	15 (3%)	240 (48%)
4	Flash purification	1 g	120 g	15 µm	450 (45%)	200 (20%)	350 (35%)
5	manual	500 mg	40 g	40-63 µm	100 (20%)	230 (46%)	170 (34%)

All the separation tests were carried out with the following stepwise gradient of PE/DCM (v/v): 2 CV at 100% PE, 7 CV at 20% DCM, 10 CV at 30% DCM and 15 CV

at 50% DCM. In all cases, three fractions were collected corresponding to the fast eluting diastereoisomer (F1), the mixture of the two diastereoisomers (F2) and the low eluting diastereoisomer (F3). Among the separation conditions tested, the best results were obtained in entry 3 with a silica mass of 80 g and a granulometry of 40 µm giving the highest ratio of separation between the fast and low eluting diastereoisomers, 49% versus 48%, respectively.

In order to identify the diastereoisomer recovered in F1 and F3, removal of the resolving agent was accomplished with LiOH in THF/H_2O (Scheme 1) and gave after a rapid purification on silica gel the corresponding pure enantiomer of cis-4-*O*-TBS-cyclopent-2-enol in high yield (95%).



Scheme 1: Identification of enantiomers

Then, the specific rotatory power value of each enantiomer was determined and compared with the previously reported data from the literature for (–)-(1*R*,4*S*)-4-((tert-butyldimethylsilyl)oxycyclopent-2-enol [4b] and (+)-(1*S*,4*R*)-4-((tert-butyldimethylsilyl)oxycyclopent-2-enol [8]. Thus, the fast eluting diastereoisomer (F1) led after deprotection to (–)-(1*R*,4*S*)-4-*O*-TBS-cyclopent-2-enol while the low eluting

diastereoisomer (F3) afforded after identical treatment the (+)-(1*S*,4*R*)-4-*O*-TBS-cyclopent-2-enol.

Conclusion

We have developed an efficient and straightforward procedure for the chemical desymmetrisation of cis-(±)-4-O-TBS-cyclopent-2-enol, using (*R*)-(+)-*O*-mandelic acid as resolving agent, affording in two steps their corresponding cis-(–) and cis-(+) enantiomer, in 43% and 42% overall yield, respectively. Furthermore, our methodology, free from the use of biocatalysts or catalysts, can give readily access to the preparation of other compounds of interest such as enantiommerically pure protected (–)- or (+)-4-hydroxycyclopent-2-enone [5, 9] following an oxidation step as previously reported [10].

Supporting Information

Supporting Information File 1:

General protocols and Spectra of compound

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