Tetrahedron Letters 55 (2014) 853–856

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoselective hydrogenation of methylcyclohex-2-ene-1,4-diols used in the synthesis of ampelomins and deoxy-carbasugars

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ARTICLE INFO

Article history:
Received 7 October 2013
Revised 7 December 2013
Accepted 9 December 2013
Available online 14 December 2013

Keywords:
Stereoselective hydrogenation
Trisubstituted cycloalkenes
Bis-allylic diols
Natural products

ABSTRACT

Stereoselective hydrogenation of methylcyclohex-2-ene-1,4-diols used as important intermediates for the preparation of ampelomins and deoxy-carbasugars was studied. These olefins were obtained in few steps from a chiral *cis*-diol resulting from microbial oxidation of toluene. Although the stereoselective hydrogenation of this type of substrates is difficult, high yields were obtained for heterogeneous hydrogenation using Adam's catalyst, where steric hindrance controlled the stereochemical outcome of the process. On the other hand, for homogeneous hydrogenation of similar olefins using Crabtree's catalyst, coordination with the allylic alcohols allowed for a controlled hydrogen addition from the more hindered face. In this manner two protocols for the hydrogenation of these types of substrates resulting in complementary stereoselectivities are described.

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Introduction

Stereoselective hydrogenation is, to date, one of the most widely used and most reliable catalytic methods for the preparation of optically active compounds.[1] An impressive number of catalysts and ligands are known, which induce very high selectivity in homogeneous metal-catalyzed hydrogenations,[2–6] creating the impression that the stereoselective hydrogenation of alkenes is a solved problem. However, the range of olefins that can be hydrogenated with high enantiomeric excess is still limited. In fact, metal diphosphine complexes do not hydrogenate tri- or tetra substituted alkenes at useful rates unless the substrate has one or more coordinating functional groups to anchor to the metal, so facilitating catalysis.[7] Thus, asymmetric hydrogenations mediated by Rh-, Ir-, or Ru-diphosphine complexes are largely restricted to substrates with coordinating groups, such as amides, alcohols, and carbonyl derivatives, disposed in the correct orientation. For metal complexes such as Wilkinson's and Crabtree's catalysts, their success in stereoselective hydrogenations is due to their ability to bind hydrogen and the C=C double bond, as well as the coordinating group, and the ligating ability of the coordinating groups may help in predicting the outcome in cases where several groups are present.[8,9]

In this context, the hydrogenation of tri- or tetrasubstitued cycloalkenes is highly substrate dependent. In particular cyclohexene derivatives bearing one or two hydroxyls at the allylic positions (allylic or bis-allylic alcohols) have been reported to undergo catalytic hydrogenation at very different rates and selectivities, depending on the structure of the substrate.[10]

In connection to our ongoing efforts to prepare polyoxygenated natural products, our group has been working on the stereoselective hydrogenation of trisubstituted cycloalkenes bearing allylic or bis-allylic alcohols. Specifically, during our studies directed toward the chemoenzymatic synthesis of ampelomins[11a,b] and deoxy-carbasugars,[11c–e] starting from microbially generated cyclohexadienediols of type **1**,[12] we required a stereoselective route for compounds **3** and **5** (Scheme 1). Both compounds can be obtained through stereoselective hydrogenation of the corresponding methyl-substituted bisallylic cycloalkenols **2** and **4**. Herein we disclose the preparation of these cycloalkenes from a common precursor, and their stereoselective hydrogenation on either face to give **3** and **5**.

Results and discussion

The synthetic sequence for both trisubstituted cycloalkenes started with the preparation of enantiopure *cis*-diol **1** using the toluene dioxygenase-mediated oxidation of toluene. The enzymatic dioxygenation of aromatic substrates is a well-established synthetic methodology.[12] In this case, *E. coli* JM109 (pDTG601) was used as the whole-cell biocatalyst to prepare diol **1** in 23 g/L of the culture broth (Scheme 2).[13] Protection of the diol functionality with the isopropylidene group followed by acetoxyiodination using acetyl hypoiodite as source of halogen (Prévost reaction) gave the acetylated halohydrin **6a**. The regio- and stereoselectivity of the halohydrin formation were thoroughly optimized, varying the halonium donor, polarity of the medium, and temperature,

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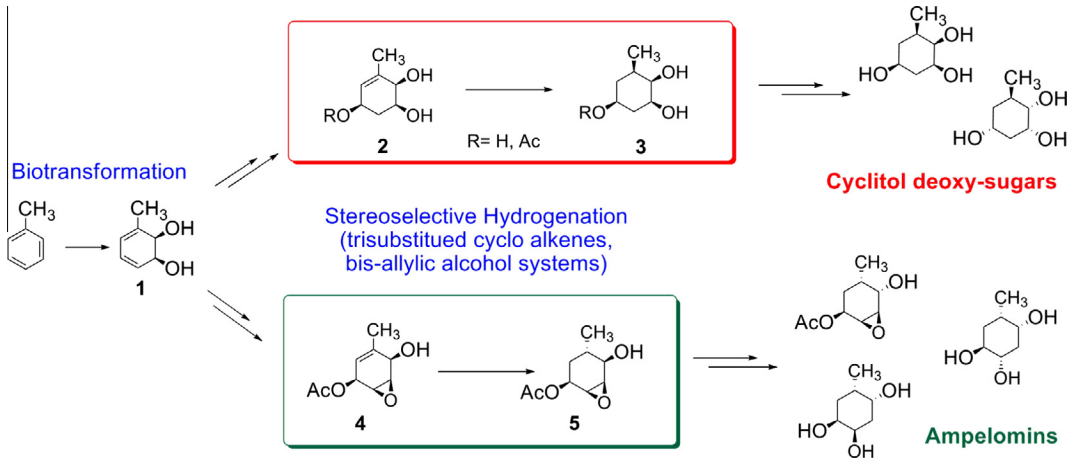
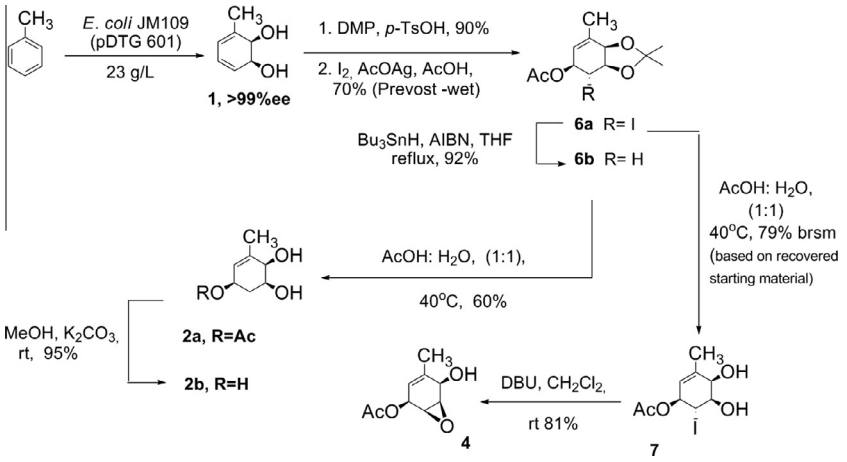
http://dx.doi.org/10.1016/j.tetlet.2013.12.036



Scheme 1. Stereoselective hydrogenation of methylcycloalkenols in route to ampelomins and deoxy-carbasugars.



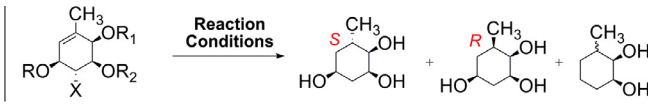
Scheme 2. Synthesis of cycloalkenes **2** and **4**.

allowing for an excellent stereoselectivity (97:3 *anti*:*syn*) and a very good regioselectivity toward the less hindered olefin (85:15).[14] Radical-mediated dehalogenation of compound **6a** followed by deprotection of the *cis*-diol in acetic acid afforded compound **2a**, which could be deacetylated in basic conditions to give triol **2b**.

With cycloalkenes **6a**, **6b**, and **2b** prepared through the aforementioned sequence, we were ready to study the stereoselective hydrogenation of the trisubstituted double bond to produce compound **3** (Table 1). In this particular case, hydrogenation must take place from the less hindered face of the ring, opposite to the oxygenated functionalities. We first tried heterogeneous hydrogenation of **6a** and **6b**, expecting a high hindering effect of the adjacent isopropylidene group, as reported in the literature for the hydrogenation of similar systems.[10a–d] As shown (entries 1–9, Table 1), the fully protected system was reluctant to hydrogenation, and in most cases (entries 3–8) the starting material was recovered unchanged after using Pd, Ni, or Adams's catalysts and a H_2 pressure up to 4 atm during 4 days. In the case of the hydrogenation of the iodine-containing alkene **6a** (entries 1 and 2) using Ni-Ra, only dehalogenation took place, without further reduction of the alkene. The heterogeneous hydrogenation was also studied over alkene **8** (entry 8), using Pd/C as catalyst during 4 days in a mixture of ethyl acetate–toluene (1:1) but no reaction took place, recovering the starting material. So we decided to remove the isopropylidene group and try hydrogenation on substrate **2b**, suspecting that some conformational rigidity could be affecting the hydrogen addition. When Adams's catalyst was used with compound **2b**, hydrogenation effectively took place, together with hydrogenolysis of the allylic C—O bond (entry 9). This result can be expected since the Lewis-acidic nature of this catalyst has been previously mentioned as a potential source of unwanted side reactions.[15] Thus, when the reaction was tried in basic medium by addition of K_2CO_3 the hydrogenation was clean, affording the saturated triol in 91% yield as a 4:1 mixture of diastereomers (entry 10). As expected, hydrogenation was directed by steric factors, resulting in the *anti* addition of the hydrogen atoms to the hydroxyl groups. Again in agreement with the literature,[10g] this kind of trisubstituted cyclic alkenes, constituting a bis-allylic alcohol system, was difficult to hydrogenate, but we found that PtO_2 with K_2CO_3 is a good choice for the hydrogenation of the fully deprotected isomer **2b**.

In addition the other alkene substrate, **4**, important for ampelomin preparation, could also be obtained from compound **6a** in a two-step sequence (Scheme 2). In this case the deprotection of the isopropylidene derivative in acetic medium had to be carefully monitored, since the competitive deacetylation was evident at prolonged reaction times. Thus, the reaction was quenched before completion, giving the diol in 79% yield based on recovered starting material (brsm). The closure to the β-epoxide **4** proceeded uneventfully using basic conditions at room temperature. Thus, the alkene **4** was obtained in four steps from diol **1** in 40% overall yield. The preparation of **5** requires hydrogen addition to the olefin

Table 1
Stereoselective heterogeneous hydrogenation



2b, R=H, X=H, R_1=R_2=H
6a, R=Ac, X=I, R_1=R_2= C(Me)$_2$
6b, R=Ac, X=H, R_1=R_2= C(Me)$_2$
8, R=H, X=H, R_1=R_2= C(Me)$_2$

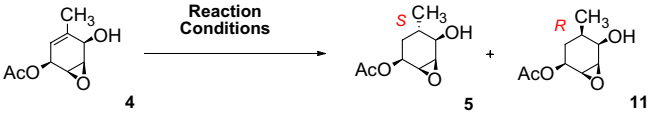
Entry	Substrate	Reaction conditions					Compound and yield
		Catalyst	Weight (%)	Solvent and d base	H_2 pressure (atm)	Time (days)	
1	**6a**	Ni Raney	10	MeOH	1	1	**6b**, 10%
2		Ni Raney	10	MeOH	4	1	**6b**, 10%
3		Pd/C	5	AcOH	4	4	**6a**, no reaction
4	**6b**	Ni Raney	10	MeOH	1	4	**6b**, no reaction
5		Pd/C	5	AcOEt:Ph (1:1)	4	4	**6b**, no reaction
6		Pd/C	10	AcOH:Hexane (1:2)	4	4	**6b**, no reaction
7		PtO_2	10	MeOH	4	4	**6b**, no reaction
8	**8**	Pd/C	10	AcOEt:Ph (1:1)	4	4	**8**, no reaction
9	**2b**	PtO_2	5	MeOH	4	0.2	**9**, 9%; **3b**, 36%; **10**, 38%
10		PtO_2	5	MeOH, K_2CO_3 (cat)	4	0.2	**9**, 18%; **3b**, 73%

through the same face of the oxygen functionalities of **4**, so we decided to use coordinating metal species like Wilkinson's or Crabtree's catalysts.[16]

Consequently, homogenous hydrogenation studies were performed with both catalysts, and the results are shown in Table 2. The starting material was recovered unchanged when using 5% and 15% molar of Wilkinson's catalyst, under 1 and 4 atm of H_2 in CH_2Cl_2 or MeOH (entries 1, 3, and 4). Increasing the catalytic load to 20% molar led to some hydrogenation under 4 atm of H_2 in CH_2Cl_2, to afford the desired compound **5** in very low yield (10% brsm over 5 days, entry 2). In turn, when using MeOH as solvent (entries 5 and 6) the corresponding epimer **11** was obtained exclusively, also in low yield (up to 10% brsm over 3 days and up to 18% brsm over 7 days). This outcome can be explained considering the coordinating effect of the solvent that prevents catalyst interaction with the substrate's oxygens allowing hydrogen addition to take place from the less hindered face. Due to the observed difficulties for getting good conversions we decided to use a more electrophilic catalytic species. This strategy was successful since when the reaction was performed using Crabtree's catalyst (20% molar) in CH_2Cl_2 and up to 4 atm of H_2 pressure during 11 days, compound **5** was obtained in 40% yield based on recovered starting material, (entry 7). Finally, best results for hydrogenation were achieved using a catalytic load of 25% molar under 4.5 atm of H_2 in CH_2Cl_2, over 10 days, (entry 8). Attempts to improve the yield by increasing further the H_2 pressure were not made in order to avoid using non-standard hydrogenation equipment. In these conditions compound **5** was prepared in 90% yield brsm.

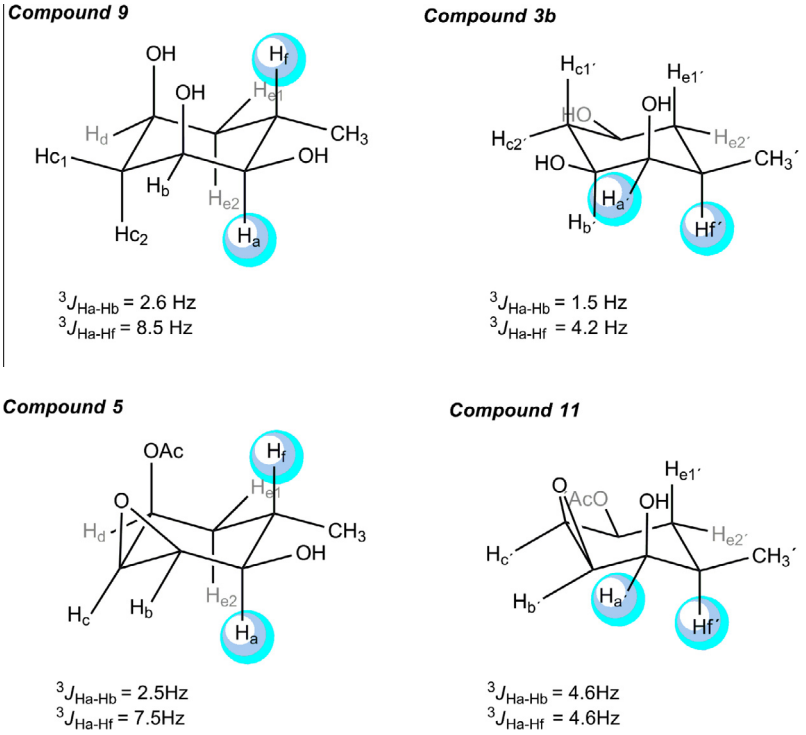
Spectroscopic data for compounds **3b**/**9** and **5**/**11** showed that they were epimers at the carbon bearing the methyl group. Stereochemical assignments were made using information from coupling constants, and comparing these values to those from similar compounds reported recently by Boyd et al.[10a,17] Thus, vicinal coupling constants for Ha and Hf (see Scheme 3) were 8.5 and 7.5 Hz for compounds **9** and **5**, respectively, indicative of a diaxial relationship. Also, the corresponding coupling constants for compounds **3b** and **11** were 4.2 and 4.6 Hz, respectively, indicative of an equatorial-axial relationship.[10a,17] In addition, for compounds **5** and **11** the assignment was confirmed by NOE experiments and NMR shift reagents (Eu(fod)$_3$), see Supporting information.

Table 2
Stereoselective homogeneous hydrogenation



Entry	Reaction conditions					Compound and yield
	Catalyst	Molar(%)	Solvent	H_2 pressure (atm)	Time (days)	
1	Wilkinson's	5	CH_2Cl_2	1	1	**4**, no reaction
2	Wilkinson's	20	CH_2Cl_2	4	5	**5**, 10% (brsm)[b]
3	Wilkinson's	15	MeOH	1	5	**4**, no reaction
4	Wilkinson's	15	MeOH	4	5	**4**, no reaction
5	Wilkinson's	20	MeOH	4	3	**11**, 10% (brsm)[b]
6	Wilkinson's	20	MeOH	4	7	**11**, 18% (brsm)[b]
7	Crabtree's[a]	20	CH_2Cl_2	4	11	**5**, 40% (brsm)[b]
8	Crabtree's	25	CH_2Cl_2	4.5	10	**5**, 90% (brsm)[b]

Wilkinson's catalyst = $(PPh_3)_3RhCl$; Crabtree's catalyst = $Ir(cod)py(PCy_3)PF_6$.
[a] Added in two portions.
[b] brsm = based on recovered starting material.



Scheme 3. Experimental values for coupling constants of epimeric pairs **3b**/**9** and **5**/**11**.

Conclusions

In summary we studied the stereoselective hydrogenation of compounds **2b** and **4** to afford useful intermediates for the preparation of ampelomins and deoxy-carbasugars. Two protocols for the hydrogenation of these types of unreactive substrates resulting in complementary stereoselectivities are described. Compounds **3b** and **5** are key intermediates for synthetic routes to deoxy-carbasugars and ampelomins, respectively; moreover triol **3b** is 2-deoxy-carba-β-L-fucose and acetate **5** is acetyl 4-*epi*-ampelomin B. Further work in this area will be published in the near future.

Acknowledgments

Support of this work from CSIC, (Universidad de la República, Uruguay) is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.036.

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