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Functionalization of natural drimanic compounds via microbial/chemical tandem reactions

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Abstract

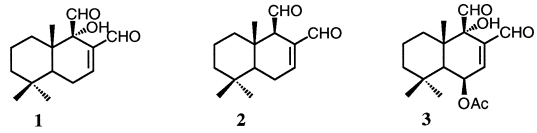
The direct microbial 3β-hydroxylation of drimanic terpenes by filamentous fungi, followed by a transfer of the functionalization from the 3β- to the 1α-position has been used for preparing derivatives of antifeedant terpenic compounds bearing an additional 1α-hydroxyl group. The semisynthesis of 1α-hydroxypolygodial is described as an example.

Keywords: Terpenes; 3β-Hydroxylation; 1α-Hydroxylation; Polygodial; Cinnamodial; Warburganal; Forskolin; Scalaradial; *Aspergillus niger*

1. Introduction

Much attention has been paid to the synthesis of active drimanes due to their wide range of biological activities and their possible industrial applications. These natural products have for example highly specific antifeedant activity to some insect species and are biodegradable molecules, which do not accumulate in the environment. Well-known examples are warburganal **1** [1,2], polygodial **2** [3,4], or cinnamodial **3** [5] which present a dialdehyde unsaturated B-ring unit as a common structural moiety (Scheme 1).

On the other hand, we have recently described [6–8] a high yield 3β-hydroxylation reaction of terpenic compounds mediated by some microorganisms. Starting from such 3β-hydroxy derivatives, it is then possible to introduce chemically in two more steps (Scheme 2) the 1α-hydroxy group [9,10], which could not be generated directly (either chemically or mi-



Scheme 1.

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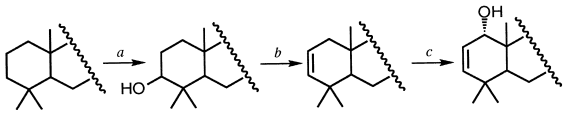
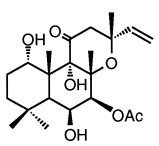


Scheme 2.

crobiologically) on the unfunctionalized substrate.

It is thus possible to associate in a single molecule both structural features (dialdehyde unsaturated B-ring and 1α-hydroxy group) [11] and to build terpenic derivatives which may have potential new activities. Forskolin **4** itself, a potent inhibitor of adenylcyclase [12], is a natural example of such derivatives and recently, a new metabolite of a sponge, scalaradial **5**, has been isolated [13] and shown to have significant cytotoxic activity.



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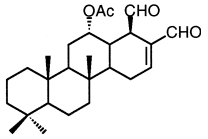

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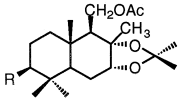
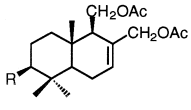
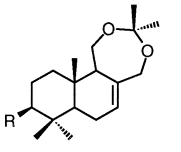
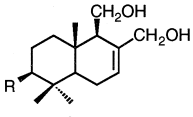
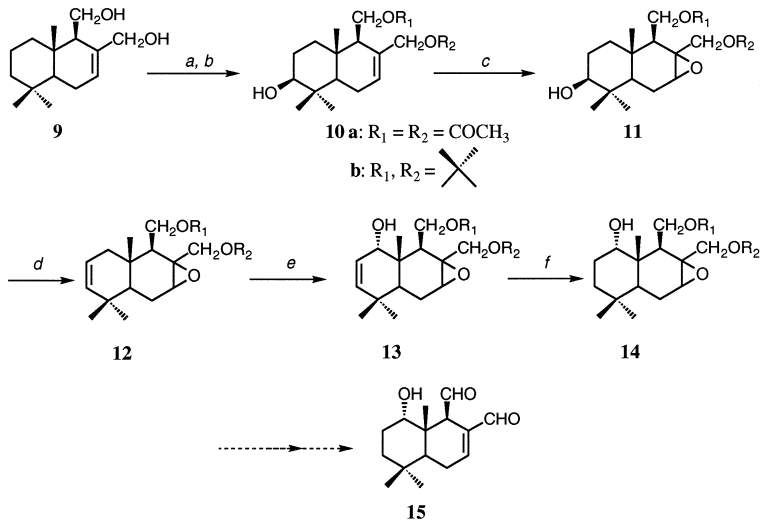
2. Experimental

Culture and incubation conditions for microorganisms have been previously described

Table 1
Microbial 3β-hydroxylation of drimanic compounds

Substrates	Microorganisms	Yield [a] of 3β-OH derivative (R = OH)	Comments
 **6** R = H	*Aspergillus niger* (ATCC 9142)	85-90%	Ref [10]
 **7** R = H	*A. niger* (ATCC 9142)	-	Untractable mixture of hydrolyzed compounds
	Rhizopus arrhizus (ATCC 11145)		Poor yield of 3β-OH diacetate
	Mucor plumbeus (ATCC 4740)		
 **8** R = H	*A. niger* (ATCC 9142)	83% (3β,11,12-triol)	-
	M. plumbeus (ATCC 4740)	-	Starting material partially recovered. Minor various triols and 3β,6α,11,12-tetrol (1-2%) isolated
 **9** R = H	*A. niger* (ATCC 9142)	81% [b]	-
	M. plumbeus (ATCC 4740)	-	Starting material partially recovered. Minor 6α,11,12-triol and 3β,6α,11,12-tetrol isolated

[a] Isolated yields.
[b] After conversion of the crude 3β,11,12-triol to isolated diacetate or acetonide derivatives.



Scheme 3. (a) Microbial hydroxylation with *A. niger* ATCC 9142 (b) DBU, *N*-acetylimidazole in CH_2Cl_2 (for **10a**) or $(CH_3)_2C(OCH_3)_2$, PPTs in CH_2Cl_2 (for **10b**); quantitative yields. (c) MCPBA in CH_2Cl_2; quantitative yields; α/β epoxide ratios: **11a,** 2:8; **11b**, 100:0. (d) Mistunobu reaction [9]; 70–75% yield from **11a**, 25–30% from **11b**. (e) SeO_2, pyridine *N*-oxide [10]; 40% yield (15% of **12** recovered). (f) H_2/PtO_2, 15 psi; quantitative yield.

[6–8]. Monitoring of the biotransformation course was performed by GC-MS using an Ultra-2 capillary column (Hewlett-Packard). Biotransformation products were extracted from incubation media by shaking three times overnight with CH_2Cl_2, then purified by silicagel chromatography. Structures were assigned by mass spectrometry, ^{1}H- and ^{13}C-NMR analysis and comparison with related compounds.

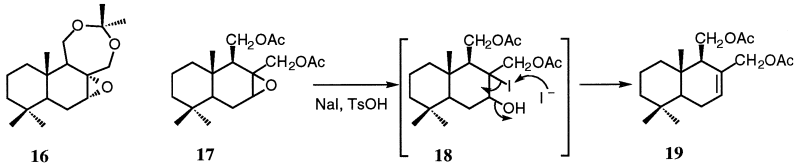
3. Results and discussion

3.1. 3β-Hydroxylation of drimanic compounds

Among the various substrates tested for microbial hydroxylation (Table 1), excellent results were obtained with the substituted derivative **6** [10], where the double bond was protected as a diol-ketal derivative, and with the simple unsaturated diol **9**, both obtained from the drimanic compounds of the terpenoid fraction extracted from the Chilian tree *Drimys winteri* Forst [14,15]. The acetonide protected diol **8** was also a good substrate, but was partially deprotected during the incubation course.

3.2. Application to a semisynthetic approach of 1α-hydroxypolygodial

The 3β-hydroxy diols **10a** or **10b** obtained by microbial hydroxylation were used as starting compounds for a semisynthetic approach of 1α-hydroxypolygodial **15**. The main difficulty originated in the presence of a 7,8-double bond in the projected final molecule. The temporary



Scheme 4.

protection of the double bond was secured by an epoxide formation (Scheme 3). However, this type of derivative proved to be relatively unstable, particularly in longer chromatographic steps. The transfer of the hydroxyl group from the 3β- to the 1α-position was carried out on the epoxides derived from **10a** or **10b** (Scheme 3), as previously described for the diol-ketal **6**.

The crucial step (not yet achieved) should be the regeneration of the 7,8-double bond. Studies have been undertaken, using model compounds **16** and **17** deriving from the diol **9**, to give the dehydro compound **19** (Scheme 4). The diacetate **17** gave appreciable results (about 35% yield) using a reaction with NaI/TsOH (or camphorsulfonic acid) in acetonitrile at room temperature [16]. Application of this method to the diacetate **14a**, followed by deprotection and oxidation of the primary alcohol groups should give the desired 1α-hydroxypolygodial **15**.

4. Conclusion

We have shown that our recently described triptycal synthesis of 1α-hydroxy terpene derivatives can be easily applied in the family of drimanic compounds, starting from a regio- and stereoselective microbial hydroxylation, to obtain new composite derivatives. This methodology can be extended to a number of other derivatives of natural terpenic substrates, in order to obtain useful synthetic units or new bioactive substances.

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