Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2013–2018

TETRAHEDRON: *ASYMMETRY*

Microbiologically-assisted hemisynthesis of 1α-hydroxydrimenol

Gérard Aranda,[a] Manuel Cortés,[b] Michèle Maurs[c] and Robert Azerad[c,*]

[a]*Laboratoire de Synthèse Organique, UMR 7652, Ecole Polytechnique, 91128 Palaiseau Cedex, France*
[b]*Pontificia Universidad Catolica de Chile, Facultad de Quimica, Casilla 306, Correo 22-Santiago, Chile*
[c]*Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques, UMR 8601, Université René Descartes-Paris V, 75006 Paris, France*

Received 4 July 2001; accepted 7 August 2001

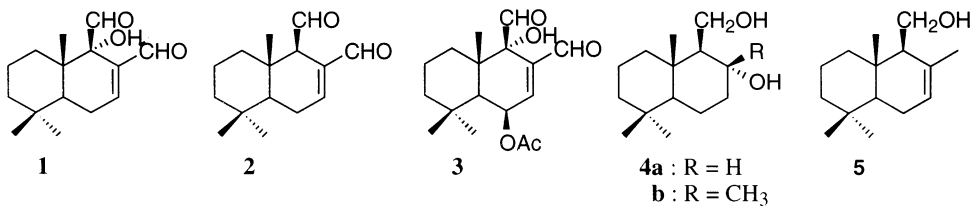
Abstract—The hemisynthesis of 1α-hydroxydrimenol has been selected to illustrate a synthetic route involving an initial microbial 3β-hydroxylation of a drimenol derivative followed by a functionalization transfer to position 1α, thus generating a new potentially bioactive hydroxylated terpenic compound. Several methods have been investigated for the protection and the regeneration of the 7,8-double bond of drimenyl derivatives. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Microbial hydroxylations have been frequently employed to achieve the selective functionalization of unactivated saturated carbon atoms, a difficult challenge using chemical methods.[1–3] Hydroxylation of terpenoid compounds has been occasionally but repeatedly reported[4–6] mainly in view of the use of the resulting derivatives as fragrance or flavor agents.[4,7,8] However, the pool of natural terpenoid compounds represents a unique and inexpensive source of structural diversity for the preparation of asymmetric synthons, hemisynthesis intermediates and chiral auxiliaries, provided selective functionalizations could be realized.

Much attention has been paid to the synthesis of hydroxylated drimanic compounds due to their wide range of biological activities and possible industrial applications. Some of 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 (Scheme 1) are warburganal **1**,[9,10] polygodial **2**,[11,12] or cinnamodial **3**,[13] which present a dialdehyde/unsaturated B-ring unit as a common structural moiety and have been the subject of continuous synthetic efforts. Other oxidized drimanic compounds, such as the drimane diols **4a** and **4b** and drimenol **5** have been recently synthesized[14–19] as suitable intermediates, especially for the synthesis of Ambrox®, a commercially important constituent of ambergris fragrance.[20]

The usual 3β-hydroxylation, a high yielding microbial reaction commonly observed with most 4,4-dimethyl terpenoid compounds,[1,6] when applied to drimanic compounds, affords the expected 3β-hydroxy derivatives,[21–27] sometimes naturally occurring in small amounts in plants or fungi. On the other hand, though only infrequently encountered, hydroxylation at the 1α-position is a distinctive feature of several other natural bioactive terpenic compounds, such as forskolin



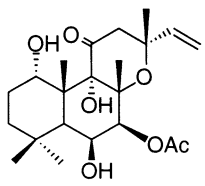
1 **2** **3** **4a** : R = H **b** : R = CH_3 **5**

Scheme 1.

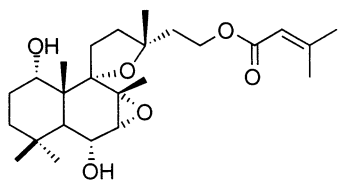
* Corresponding author. Tel.: +33 (0)1 42 86 21 71; fax: +33 (0)1 42 86 83 87; e-mail: azerad@biomedicale.univ-paris5.fr

PII: S0957-4166(01)00353-6

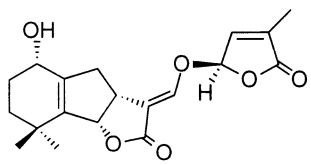
6, a potent inhibitor of adenylcyclase,[28] erigerol **7**,[29] or (+)-strigol **8**.[30,31] Several 1-hydroxyditerpenes with weak cytotoxic activities have been recently isolated from liverworts.[32] Moreover, 1α-hydroxylated drimanes may represent a simplified structural pattern[33] of recently found new sesterpene metabolites of marine sponges[34–36] such as scalaradial **9**, which have been shown to have significant cytotoxic activity. Such a hydroxylation position is rarely obtained in significant amounts by microbial methods whatever the microorganism used.[37–41] However, starting from 3β-hydroxy derivatives, we have previously shown that a simple reaction sequence can result (in only three more steps) in a functionalization transfer which allows the preparation of 1α-hydroxylated compounds in good yields.[25,42–44]



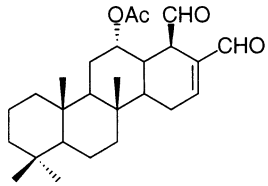
6



7



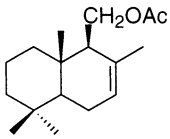
8



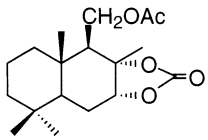
9

2. Results and discussion

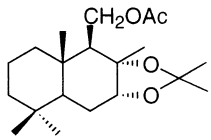
Herein, we describe the use of this reaction sequence for the hemisynthesis of 1α-hydroxydrimenol from drimenol **5**, a $\Delta^{7,8}$-unsaturated drimanic derivative isolated from the bark of *Drimys winteri* Forst. (Winteraceae), a South American tree commonly found in Chile and Argentina.[9] In contrast to other drimenic (lactonic) compounds of the same origin, which present a relatively inert double bond in position-8,9, such as confertifolin or isodrimenin,[26,44] the presence of a 7,8-double bond in drimenol **5** and the corresponding derivatives (drimenin, cinnamolide, for example) does introduce an additional complexity in the proposed synthetic route, which involves an intermediate allylic oxidation and a catalytic reduction, and thus necessitates the protection and regeneration of the 7,8-double bond.



10



11



12

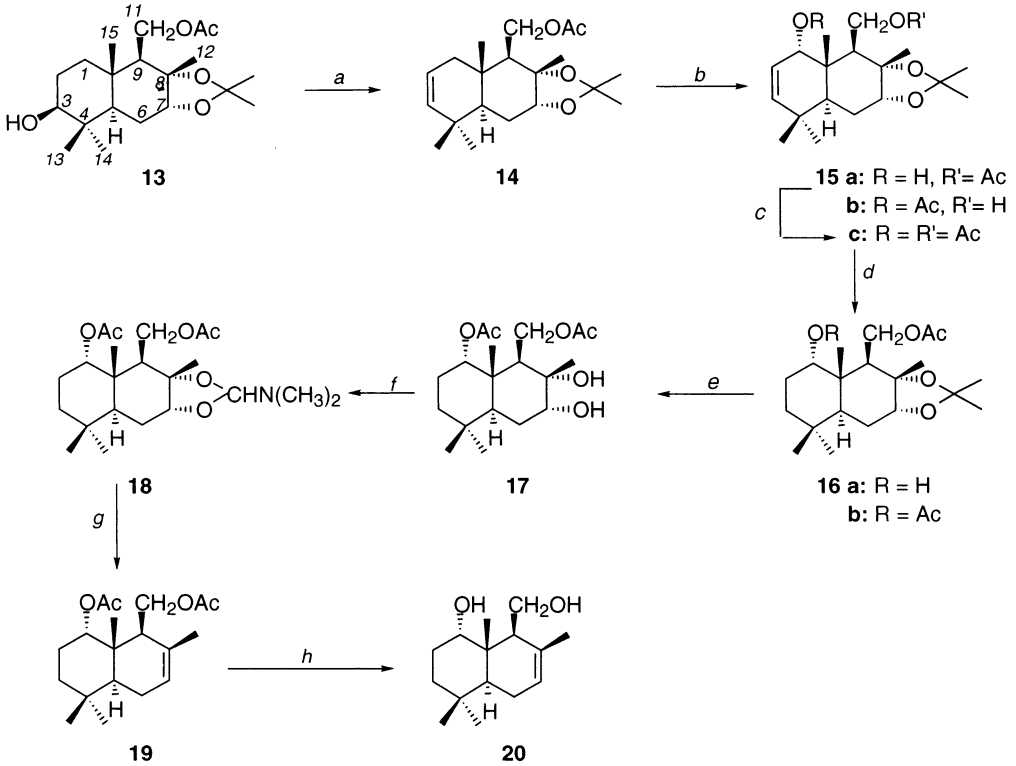
Previous studies into the microbial hydroxylation of drimenol **5** or its acetate ester **10** have pointed up the low yields obtained, attributed to solubility problems. These were partially circumvented by using β-cyclodextrin complexation[23] to give a maximum conversion yield of 33% into its 3β-hydroxy derivative. On the contrary, derivatives **11**–**12**, designed for masking the double bond,[43,45] afforded higher yields of the corresponding 3β-hydroxylated compounds, as shown in Table 1. Near quantitative yields were reproducibly obtained with the 7α,8α-dihydroxy acetonide **12**.[45]

From the 3β-hydroxy-7,8-acetonide **13**, a chemical strategy was developed for a subsequent hydroxyl transfer to the 1α-position, then regeneration of the 7,8-double bond (Scheme 2). The simultaneous presence of the 2,3 and 7,8 unsaturations had to be avoided, as allylic oxidation with SeO_2[21,46,47] preferentially occurs on the 9α-position and no selective hydrogenation method[33,48] is available. After 2,3-dehydration and SeO_2 oxidation, the 1α-hydroxy isopropylidenedioxymonoacetate **15a** underwent partial acetyl transfer from the primary 11-position to the 1α-position, and subsequent hydrogenation of the mixture of monoacetyl derivatives **15a** and **15b** afforded the corresponding mixture of saturated derivatives, from which the 1α-hydroxy-11-acetyl compound **16a** could be obtained in low yield by repeated chromatography. Therefore, the mixture of 1α- and 11-monoacetylated-2,3-unsaturated compounds was fully acetylated, then hydrogenated to give **16b**. Quantitative hydrogenation was only obtained by using PtO_2 in EtOAc at room temperature. Other catalysts (Pd on charcoal or Crabtree's catalyst) were found to be ineffective.

Deprotection of the isopropylidene function using standard acidic reagents at 0°C was not chemoselective,

Table 1. Bioconversion yields of drimenol derivatives into the corresponding 3β-hydroxylated compounds

	Microorganism	Bioconversion time	Isolated yield (%)	Ref.
Drimenol **5**	*Aspergillus niger*	6 days	2	[23]
	Mucor plumbeus	26–28 h	7	
	Rhizopus arrhizus	29 h	60	
Drimenyl acetate **10**	*A. niger*	6 days	10	[23]
	A. niger + Carbopol 934	6 days	18	
	A. niger + Carbopol 934 + β-cyclodextrin	6 days	33	
7α,8α-Dihydroxydrimanyl acetate	*A. niger* ATCC 9142	2 days	5	–
7α,8α-Dioxycarbonyldrimanyl acetate **11**	*A. niger* ATCC 9142	3 days	35–40	–
7α,8α-Isopropylidenedioxydrimanyl acetate **12**	*A. niger* ATCC 9142	4 days	70–85	[43]



Scheme 2. (a) Ph_3P/THF, NaPTS, reflux; (b) SeO_2, pyridine *N*-oxide/dioxane, 100°C; (c) Ac_2O–Et_3N, DMAP/CH_2Cl_2; (d) H_2–PtO_2/EtOAc; (e) $CuCl_2{\cdot}2H_2O$/MeCN; (f) $Me_2NCH(OMe)_2$, 4°C, 24 h; (g) Ac_2O, 130°C; (h) 1N KOH/dioxane.

whatever the reagent or solvent used. In all cases the 11-acetyl function was also partially or completely deprotected. A slow but clean and chemoselective deprotection was obtained by applying the recently described protocol[49] using $CuCl_2{\cdot}2H_2O$ in acetonitrile at room temperature. The diol **17** was obtained in 85% yield and submitted to known methods for the regeneration of the 7,8-unsaturation. The Corey–Winter method[50,51] utilizing a 7,8-thionocarbonate gave poor results due to difficulties in separating the product from triethyl phosphite by-products. However, the method proposed by Hanessian,[52] starting from *N*-dimethylaminomethylenedioxy derivative **18** and heating in acetic anhydride, provided the 7,8-unsaturated diacetate **19**, which was then subjected to an easy and quantitative hydrolysis to give the expected 1α-hydroxy drimenol **20** in an overall 34% yield (calculated from **13**).

3. Conclusion

In conclusion, the described hemisynthesis of the new 1α-hydroxy derivative of drimenol illustrates the potential of a combined chemoenzymatic approach involving the necessary protection and regeneration of a double bond. Extension of this strategy to obtain rapid access to other terpenoid derivatives is currently being investigated. A study of the potential biological activities of some of the synthesized products is currently in progress.

4. Experimental

4.1. General

General experimental methods have been described earlier.[27,38,43] High resolution mass spectrometry (HRMS) was performed on a JEOL MS700 spectrometer. EI- and CI-MS were performed on a Hewlett–Packard 5989B instrument. Incubation course was monitored by GC–MS using a 25 m×0.2 mm Ultra 2 (Hewlett–Packard) capillary column (temperature programmed 110–270°C at 8°C min^{-1}). Column chromatography was performed on a silica gel Merck 60H (70–230 mesh).

4.2. Starting materials

Drimenol was isolated from the petroleum ether fraction of the bark of *Drimys winteri* Forst[53] and converted to the corresponding acetate **10**, the 7α,8α-dihydroxy derivative, and the 7α,8α-isopropylidenedioxy-11-acetate derivative **12** as previously described.[23,45] ^{13}C Chemical shifts are given in Table 2 for completion of earlier spectroscopic data.

The cultivation and incubation of fungal strains with drimanic substrates have been previously described.[22,26] Substrate **12** (0.5 g L^{-1}) was incubated with 65 h-grown cultures of *Aspergillus niger* at 27°C for 4 days. Bioconversion mixtures were extracted 3–4 times with CH_2Cl_2

Table 2. ^{13}C NMR chemical shifts of intermediates **11**–**20** (50.323 MHz, δ ppm in $CDCl_3$). Multiplicity was determined by DEPT experiments

Carbon no.	**11**	**12**	**13**	**14**	**15a**	**16a**	**16b**	**17**	**19**	**20**
1	39.4	38.8	37.3	39.2	71.6	71.1	74.1	74.0	74.5	72.0
2	18.4	18.3	27.2	120.9	119.9	24.7	22.6	22.0	23.7	25.7
3	41.8	41.8	78.5	137.7	143.0	34.7	35.0	35.1	34.7	34.3
4	32.6	32.7	38.5	34.0	34.6	32.7	32.5	32.5	32.7	32.9
5	45.9	47.1	46.7	43.6	37.6	39.4	40.1	40.7	44.4	44.0
6	25.9	23.2	23.1	23.1	23.2	22.9	22.1	25.7	22.7	24.1
7	73.7	80.1	80.2	79.9	79.8	80.0	80.0	73.7	123.2	123.0
8	73.5	80.4	80.4	80.3	80.7	80.9	80.9	73.8	132.1	132.6
9	54.4	54.6	54.8	52.7	43.5	47.0	45.5	45.5	44.8	49.1
10	37.8	37.3	37.3	36.4	39.2	41.5	35.0	39.3	39.3	40.2
11	62.6	61.6	61.6	61.6	61.7	62.3	61.6	62.3	62.7	60.3
12	23.5	22.2	22.2	21.5	21.5	22.9	21.9	23.6	21.9	22.4
13	21.5	21.4	15.1	23.7	23.2	22.3	21.7	21.7	22.3	22.0
14	33.1	33.2	28.0	31.5	31.0	32.9	33.0	33.0	33.2	33.1
15	15.3	15.2	15.2	15.2	14.0	15.2	14.5	15.3	14.3	14.4
$COCH_3$	–	171.0	170.8	170.9	171.1	171.0	171.2	171.5	170.2	–
		21.3	21.1	21.3	21.1	21.2	170.4	170.4	170.9	
							21.1	21.1	21.1	
								21.6	21.3	
$(CH_3)_2C$	–	107.0	107.2	107.2	107.4	107.3	107.2	–	–	–
		28.4	28.4	28.4	28.3	28.5	28.3			
		27.3	27.3	27.3	27.4	27.3	27.4			

(v/v) at room temperature under vigorous stirring for 24 h. After pooling and evaporation in vacuo, the crude extract was chromatographed over silica gel to provide successively 3-keto-7α,8α-isopropylidenedioxy-11-acetoxydrimane (5–12%) and 3β-hydroxy-7α,8α-isopropylidenedioxy-11-acetoxydrimane **8** (70–85%).

4.3. 3-Keto-7α,8α-isopropylidenedioxy-11-acetoxydrimane

Mp 126°C (crystallized from CH_2Cl_2–pentane). $[\alpha]_D^{20}$ −49.4 (MeOH, *c* 0.47). IR (CCl_4) cm^{-1}: 2985, 2873, 1741, 1711, 1454, 1381, 1368, 1239, 1179, 1124, 1082, 1032. ^1H NMR, δ ppm ($CDCl_3$): 1.03, 1.04 and 1.09 (9H, 3s, 13-, 14- and 15-CH_3), 1.25 (3H, s, 12-CH_3), 1.32 and 1.42 (6H, 2s, $(CH_3)_2CO$), 2.0 (3H, s, $COCH_3$), 2.32 and 2.65 (AB part of an ABXY system with H_2-1, $J_{AB}=15.5$, $J_{AX}=5.3$, $J_{AY}=3.2$, $J_{BX}=13.3$ and $J_{BY}=6.4$ Hz, H_2-2), 3.97 (1H, t, $J=2.5$ Hz, 7β-H), 4.21 and 4.31 (2H, AB part of an ABX system with H-9α, $J_{AB}=11.8$, $J_{AX}=3.8$, $J_{BX}=6.75$ Hz, H_2-11). ^{13}C NMR, see Table 2. CI-HRMS (NH_3), calcd for $C_{20}H_{33}O_5$ $(M+1)^+$: 353.2328; found: 353.2324.

4.3.1. 3β-Hydroxy-7α,8α-isopropylidenedioxy-11-acetoxydrimane 13. Mp 81–82.5°C. $[\alpha]_D^{21}$ −23 (MeOH, *c* 2.0); −23.4 ($CDCl_3$, *c* 1.13). IR (CCl_4) cm^{-1}: 3464, 2980, 2935, 2869, 1738, 1463, 1381, 1367, 1246, 1080, 1034, 994, 912. ^1H NMR, δ ppm ($CDCl_3$): 0.79, 0.85 and 1.02 (9H, 3s, 13-, 14- and 15-CH_3), 1.23 (3H, s, 12-CH_3), 1.34 and 1.45 (6H, 2s, $(CH_3)_2CO$), 2.02 (3H, s, $COCH_3$), 3.30 (1H, dd, $J=10.3$ and 5.0 Hz, 3α-H). 3.94 (1H, t, $J=7.9$ Hz, 7β-H), 4.16–4.31 (2H, AB part of an ABX system with H-9α, $J_{AB}=11.6$, $J_{AX}=3.7$, $J_{BX}=6.8$ Hz, H_2-11). ^{13}C NMR, see Table 2. CI-HRMS (NH_3), calcd for $C_{20}H_{35}O_5$ $(M+1)^+$: 355.2484; found: 355.2480.

4.3.2. 7α,8α-Isopropylidenedioxy-11-acetoxydrim-2-ene 14. Following an earlier described protocol,[42,43] 3β-hydroxy-7α,8α-isopropylidenedioxy-11-acetoxydrimane **13** (0.52 g) and triphenyl phosphine (1.53 g) were carefully dried in vacuo at 40°C then dissolved into freshly distilled THF (18 mL). DEAD (0.52 mL) was added with stirring under a nitrogen atmosphere. After stirring under reflux for 1 h, sodium *p*-toluene sulfonate (0.90 g) was added in one portion and the mixture stirred under reflux for a further 15 min. After cooling and removal of THF under vacuum, the residue was dissolved in CH_2Cl_2 and chromatographed on silica gel to give **14** as a colorless oil (0.428 g, 87%). $[\alpha]_D^{21}$ −10.9 (MeOH, *c* 2.0). IR (CCl_4) cm^{-1}: 2984, 2934, 1740, 1453, 1379, 1366, 1244, 1208, 1081, 998. ^1H NMR, δ ppm ($CDCl_3$): 0.88, 0.90 and 1.0 (9H, 3s, 13-, 14- and 15-CH_3), 1.26 (3H, s, 12-CH_3), 1.35 and 1.46 (6H, 2s, $(CH_3)_2CO$), 2.03 (3H, s, $COCH_3$), 2.49 (1H, dd $J=4.3$ and 6.5 Hz, 9α-H), 3.95 (1H, br.s, 7β-H), 4.26 and 4.36 (2H, AB part of an ABX system with 9α-H, $J_{AB}=11.6$, $J_{AX}=4.3$, $J_{BX}=6.5$ Hz, H_2-11), 5.40 (2H, m, H-2 and H-3). ^{13}C NMR, see Table 2. CI-HRMS (NH_3), calcd for $C_{20}H_{33}O_4$ $(M+1)^+$: 337.2379, found: 337.2382.

1α-Hydroxy-7α,8α-isopropylidenedioxy-11-acetoxydrim-2-ene **15a**, mp 56–57°C (from MeOH) and 1α-acetoxy-7α,8α-isopropylidenedioxy-11-hydroxydrim-2-ene **15b**, mp 140–143°C (from MeOH) have been previously described.[43]

4.3.3. 1α-Hydroxy -7α,8α-isopropylidenedioxy-11-acetoxy-drimane 16a. The mixture of 1α- and 11-acetoxyderivatives **15a**–**15b** (214 mg) resulting from acetyl group transfer after hydroxylation and standing was hydrogenated in ethyl acetate (15 mL) in the presence of PtO_2 (100 mg) for 7 h at room temperature to give

after usual work-up a crystalline residue, from which a mixture of 1α- and 11-acetylated derivatives (38 mg) and the hydrogenated 1α-hydroxy derivative **16a** (162 mg) were separated by repeated chromatography. Mp 84.5–86°C. $[\alpha]_D^{21}$ −3.6 (MeOH, *c* 1.66). IR (CCl_4) cm^{-1}: 3593, 3513, 2984, 2984, 2949, 1752, 1723, 1380, 1367, 1245, 1219, 1082, 1068, 1004, 994. ^1H NMR, δ ppm ($CDCl_3$): 0.80, 0.82 and 0.92 (9H, 3s, 13-, 14- and 15-CH_3), 1.24 (3H, s, 12-CH_3), 1.32 and 1.43 (6H, 2s, $(CH_3)_2CO$), 2.05 (3H, s, $COCH_3$), 2.36 (1H, dd, $J=4.7$ and 7 Hz, 9α-H), 3.52 (1H, br. s., 1β-H), 3.90 (1H, t, $J=2.9$ Hz, 7β-H), 4.14 and 4.33 (2H, AB part of an ABX system with 9α-H, $J_{AB}=11.6$, $J_{AX}=4.7$, $J_{BX}=7.0$ Hz, H_2-11). ^{13}C NMR, see Table 2. EI-HRMS, calcd for $C_{20}H_{34}O_5$ M^+: 354.2406; found: 354.2399.

4.3.4. 1α-11-Diacetoxy-7α,8α-isopropylidenedioxydrim-2-ene 15c. The mixture of acetoxy derivatives **15a**–**15b** was quantitatively acetylated with acetic anhydride–Et_3N (in the presence of a catalytic amount of DMAP) in CH_2Cl_2 to give the diacetate **15c**. Mp 57–58°C (from CH_2Cl_2–pentane). $[\alpha]_D^{20}$ +155 ($CHCl_3$, *c* 1.546). IR (CCl_4) cm^{-1}: 2984, 2937, 2868, 1741, 1453, 1379, 1368, 1252, 1187, 1086, 1030, 1012, 998, 912. ^1H NMR, δ ppm ($CDCl_3$): 0.82, 0.85 and 0.98 (9H, 3s, 13-, 14- and 15-CH_3), 1.20 (3H, s, 12-CH_3), 1.29 and 1.42 (6H, 2s, $(CH_3)_2CO$), 1.92 and 1.99 (6H, 2s, $COCH_3$), 2.59 (1H, dd, $J=5.2$ and 7.4 Hz, 9α-H), 3.87 (1H, t, $J=3.4$ Hz, 7β-H), 4.08 and 4.18 (2H, AB part of an ABX system with 9α-H, $J_{AB}=11.8$, $J_{AX}=5.2$, $J_{BX}=7.4$ Hz, H_2-11), 4.65 (1H, d, $J=5.8$ Hz, 1β-H), 5.55 and 5.72 (2H, AB part of an ABX system with 1β-H, $J_{AB}=11.0$, $J_{AX}=0$, $J_{BX}=5.8$ Hz, H-2 and H-3). ^{13}C NMR, see Table 2. CI-HRMS (NH_3), calcd for $C_{22}H_{35}O_6$ $(M+1)^+$: 395.2434; found: 395.2422.

4.3.5. 1α-11-Diacetoxy-7α,8α-isopropylidenedioxydrimane 16b. The diacetate **15c** (224 mg) in ethyl acetate (12.5 mL) was quantitatively hydrogenated in two successive operations, using, respectively, 110 and 83 mg of PtO_2 over 7 h at room temperature to give a colorless oil. $[\alpha]_D^{22}$ +9.3 (MeOH, *c* 1.92). IR (CCl_4) cm^{-1}: 2984, 2954, 2869, 1740, 1379, 1368, 1250, 1084, 1041, 1006, 978. CI-MS, *m*/*z* 397 $(M+1)^+$. ^1H NMR, δ ppm ($CDCl_3$): 0.81, 0.85 and 0.90 (9H, 3s, 13-, 14- and 15-CH_3), 1.20 (3H, s, 12-CH_3), 1.28 and 1.41 (6H, 2s, $(CH_3)_2CO$), 1.92 and 2.07 (6H, 2s, $COCH_3$), 2.50 (1H, dd, $J=7.0$ and 5.3 Hz, 9α-H), 3.85 (1H, t, $J=2.5$ Hz, 7β-H), 4.0 and 4.20 (2H, AB part of an ABX system with 9α-H, $J_{AB}=11.9$, $J_{AX}=5.2$, $J_{BX}=7.0$ Hz, H_2-11), 4.53 (1H, t, $J=2.6$ Hz, 1β-H). ^{13}C NMR, see Table 2.

4.3.6. 1α,11-Diacetoxy-7α,8α-dihydroxydrimane 17. 1α,11-Diacetoxy-7α,8α-isopropylidenedioxydrimane **16b** (190 mg) was dissolved in acetonitrile (15 mL) and stirred at room temperature with $CuCl_2{\cdot}2H_2O$ (2 equiv., 224 mg) for 53 h. The blue solution was filtered on silica gel to yield 15 mg of starting material and 140 mg (83%) of the diol **17**. Mp 58–60°C (from CH_2Cl_2–pentane). $[\alpha]_D^{22}$ +4.2 (MeOH, *c* 2.055). IR (CCl_4) cm^{-1}: 3632, 3563, 3460, 2956, 2872, 1735, 1389, 1372, 1251, 1038, 972. ^1H NMR, δ ppm ($CDCl_3$): 0.84, 0.93 and 0.94 (9H, 3s, 13-, 14- and 15-CH_3), 1.18 (3H, s, 12-CH_3), 2.0 and 2.04 (6H, 2s, $2COCH_3$), 2.32 (1H, dd, $J=3.4$ and 6 Hz, 9α-H), 3.64 (1H, s, 7β-H), 4.10 and 4.35 (2H, AB part of an ABX system with 9α-H, $J_{AB}=12.1$, $J_{AX}=6.0$, $J_{BX}=3.3$ Hz, H_2-11), 4.63 (1H, t, $J=2.7$ Hz, 1β-H). ^{13}C NMR, see Table 2. CI-HRMS (NH_3), calcd for $C_{19}H_{33}O_6$ $(M+H)^+$: 357.2277; found: 357.2270.

4.3.7. 1α,11-Diacetoxy-drim-7-ene 19. 1α,11-Diacetoxy-7α,8α-dihydroxydrimane **17** (231 mg) was dissolved in freshly distilled *N*,*N*-dimethylformamide dimethylacetal (6 mL, Eb = 102–104°C) and stirred overnight at 4°C. After evaporation under vacuum and careful drying, the *N*-dimethylaminomethylenedioxy derivative **18** was added to acetic anhydride (0.2 mL) and the mixture was heated under nitrogen for 30 min at 130°C with stirring. Extraction with ethyl ether and usual work-up yielded a colorless oil, which was purified by silica gel filtration (210 mg). After crystallization from ethyl ether–pentane, mp 60–62°C. $[\alpha]_D^{25}$ +64.6 (MeOH, *c* 1.98). IR (CCl_4) cm^{-1}: 2925, 1743, 1367, 1241, 1154, 1037, 990. CI-MS (NH_3) *m*/*z* 323 $(M+H)^+$. ^1H NMR, δ ppm ($CDCl_3$): 0.87, 0.89 and 0.91 (9H, 3s, 13-, 14- and 15-CH_3), 1.63 (3H, s, 12-CH_3), 1.98 and 2.04 (6H, 2s, $2COCH_3$), 2.60 (1H, br.dd, 9α-H), 4.06 and 4.10 (2H, AB part of an ABX system with 9α-H, $J_{AB}=13.0$, $J_{AX}=2.7$, $J_{BX}=3.4$ Hz, H_2-11), 4.96 (1H, t, $J=5.5$ Hz, 1β-H), 5.46 (1H, br.s, H-7). ^{13}C NMR, see Table 2.

4.3.8. 1α,11-Dihydroxydrim-7-ene 20. Hydrolysis of **19** (153 mg) was conducted in dioxane (10 mL) added to a 1N aqueous KOH solution (6 mL) overnight at 4°C. After neutralization with solid boric acid, the pure diol was isolated in quantitative yield by extraction with CH_2Cl_2. Mp 103–104°C (from ethyl acetate–pentane). $[\alpha]_D^{25}$ +23.1 (MeOH, *c* 1.25). IR ($CHCl_3$) cm^{-1}: 3748, 3660, 3030, 3014, 2990, 1574, 1489, 1244, 1037, 928. ^1H NMR, δ ppm ($CDCl_3$): 0.80, 0.89 and 0.90 (9H, 3s, 13-, 14- and 15-CH_3), 1.70 (3H, s, 12-CH_3), 2.63 (1H, br.dd, 9α-H), 3.78 (2H, br.m, H-11), 3.87 (1H, br.s, 1β-H), 5.42 (1H, br.s, H-7). ^{13}C NMR, see Table 2. CI-HRMS (NH_3): calcd for $C_{15}H_{27}O_2$ $(M+1)^+$: 239.2011; found: 239.2016.

Acknowledgements

We warmly thank Nicole Morin for all HRMS measurements.

References

1. Holland, H. L. *Organic Synthesis with Oxidative Enzymes*; VCH: New York, 1992.
2. Azerad, R. *Chimia* **1993**, *47*, 93–96.
3. Azerad, R. In *Asymmetric Oxidation Reactions: A Practical Approach*; Katsuki, T., Ed. Oxidations using a biocatalyst. Hydroxylation at a saturated carbon (Chapter 5.1). Oxford University Press: New York, 2001; pp. 181–200.
4. Krasnobajew, V. *Biotechnology*, *A Comprehensive Treatise*, *Vol. 6a*, *Biotransformations*; Kieslich, K., Ed. Terpenoids. Verlag Chemie: Weinheim, 1984; pp. 97–125.

5. Lamare, V.; Furstoss, R. *Tetrahedron* **1990**, *46*, 4109–4132.
6. Azerad, R. In *Stereoselective Biocatalysis*; Patel, R., Ed. Regio- and stereoselective microbial hydroxylation of terpenoid compounds. Marcel Dekker: New York, 2000; pp. 153–180.
7. Hagedorn, S.; Kaphammer, B. *Annu. Rev. Microbiol.* **1994**, *48*, 773–800.
8. Krings, U.; Berger, R. G. *Appl. Microbiol. Biotechnol.* **1998**, *49*, 1–8.
9. Kubo, I.; Lee, Y.-W.; Pettei, M.; Pilkiewicz, F.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1976**, 1013.
10. Kubo, I.; Susuki, T.; Tanemura, H.; Kumanireng, A. S.; Ototani, N.; Kitahara, Y. *Tetrahedron Lett.* **1977**, 4553.
11. Barnes, C. S.; Loder, J. W. *Aust. J. Chem.* **1962**, *15*, 322.
12. Loder, J. W. *Aust. J. Chem.* **1962**, *15*, 389.
13. Canonica, L.; Corbella, A.; Gariboldi, P.; Jommi, G.; Krepinsky, J. *Tetrahedron* **1969**, *25*, 3895.
14. Shishido, K.; Omodani, T.; Shibuya, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2285–2287.
15. Barrero, A. F.; Altarejos, J.; Alvarez Manzaneda, E. J.; Ramos, J. M.; Salido, S. *Tetrahedron* **1993**, *49*, 6251–6262.
16. Barton, D. H. R.; Taylor, D. K.; Tse, C. L. *Tetrahedron Lett.* **1994**, *35*, 9505–9508.
17. Nair, M. S.; Anikumar, A. T. *Biotechnol. Lett.* **1994**, *16*, 161–162.
18. Akita, H.; Nozawa, M.; Shimizu, H. *Tetrahedron: Asymmetry* **1998**, *9*, 1789–1799.
19. Lagnel, B. M. F.; Morin, C.; De Groot, A. *Synthesis* **2000**, 1907–1916.
20. Ohloff, G. In *Fragance Chemistry*; Thiemer, E. T., Ed.; Academic Press: New York, 1982; p. 535.
21. Hollinshead, D. M.; Howell, S. C.; Ley, S. V.; Mahon, M.; Ratcliffe, N. M.; Worthington, P. A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1579–1589.
22. Aranda, G.; Facon, I.; Lallemand, J. Y.; Leclaire, M.; Azerad, R.; Cortes, M.; Lopez, J.; Ramirez, H. *Tetrahedron Lett.* **1992**, *33*, 7845–7848.
23. Ramirez, H. E.; Cortes, M.; Agosin, E. *J. Nat. Prod.* **1993**, *56*, 762–764.
24. Herlem, D.; Ouazzani, J.; Khuong-Huu, F. *Tetrahedron Lett.* **1996**, *37*, 1241–1243.
25. Aranda, G.; Bertranne-Delahaye, M.; Lallemand, J.-Y.; Azerad, R.; Maurs, M.; Cortes, M.; Lopez, J. *J. Mol. Catal.: B. Enzym.* **1998**, *5*, 203–206.
26. Maurs, M.; Azerad, R.; Cortes, M.; Aranda, G.; Bertranne-Delahaye, M.; Ricard, L. *Phytochemistry* **1999**, *52*, 291–296.
27. Aranda, G.; Azerad, R.; Maurs, M.; Bertho, G.; Jiménez-Gonzalez, D.; Cabrera-Torres, E.; Barrero, A. F. *Phytochemistry* **2000**, *54*, 23–27.
28. Colombo, M. I.; Zinczuc, J.; Ruveda, E. A. *Tetrahedron* **1992**, *48*, 963.
29. Kienzle, F.; Stadlwieser, J.; Rank, W.; Mergelsberg, I. *Tetrahedron Lett.* **1988**, *29*, 6479–6482.
30. Cook, C. E.; Whichard, L. P.; Turner, B.; Wall, M. E.; Egley, G. H. *Science* **1966**, *154*, 1189.
31. Brooks, D. W.; Bevinakatti, H. S.; Powell, D. R. *J. Org. Chem.* **1985**, *50*, 3779.
32. Lorimer, S. D.; Perry, N. B.; Burgess, E. J.; Foster, L. M. *J. Nat. Prod.* **1997**, *60*, 421–424.
33. Tozyo, T.; Yasuda, F.; Nakai, H.; Tada, H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1859–1866.
34. Fattorusso, E.; Magno, S.; Santacroce, C.; Sica, D. *Tetrahedron* **1972**, *28*, 5993–5997.
35. Rueda, A.; Zubia, E.; Ortega, M. J.; Carballo, J. L.; Salva, J. *J. Org. Chem.* **1997**, *62*, 1481–1485.
36. Lu, Q.; Faulkner, D. J. *J. Nat. Prod.* **1997**, *60*, 195–198.
37. Nadkarni, S. R.; Akut, P. M.; Ganguli, B. N.; Khandelwal, Y.; De Souza, N. J.; Rupp, R. H. *Tetrahedron Lett.* **1986**, *27*, 5265–5268.
38. Aranda, G.; ElKortbi, M. S.; Lallemand, J. Y.; Neuman, A.; Hammoumi, A.; Facon, I.; Azerad, R. *Tetrahedron* **1991**, *47*, 8339–8350.
39. Fraga, B. M.; Gonzàlez, P.; Guillerma, R.; Hernàndez, M. G. *Tetrahedron* **1998**, *54*, 6159–6168.
40. Fraga, B. M.; Gonzàlez, P.; Hernàndez, M. G.; Suàrez, S. *Tetrahedron* **1999**, *55*, 1781–1792.
41. Fraga, B. M.; Hernàndez, M. G.; Gonzàlez, P.; Lopez, M.; Suàrez, S. *Tetrahedron* **2001**, *57*, 761–770.
42. Aranda, G.; Lallemand, J.-Y.; Azerad, R.; Maurs, M.; Cortes, M.; Ramirez, H.; Vernal, G. *Synth. Commun.* **1994**, *24*, 2525–2535.
43. Aranda, G.; Bertranne-Delahaye, M.; Azerad, R.; Maurs, M.; Cortes, M.; Ramirez, H.; Vernal, G.; Prangé, T. *Synth. Commun.* **1997**, *27*, 45–60.
44. Aranda, G.; Moreno, L.; Cortés, M.; Maurs, M.; Azerad, R. *Tetrahedron* **2001**, *57*, 6051–6056.
45. Maturana, H.; Lopez, J.; Cortés, M. *Synth. Commun.* **1991**, *21*, 1533–1543.
46. Cortés, M.; Razmilic, I.; Sierra, J. R.; Lopez, J. *Chem. Ind.* **1985**, *17*, 735.
47. Razmilic, I.; Lopez, J.; Sierra, J.; Cortés, M. *Synth. Commun.* **1987**, *7*, 95.
48. Hersel, U.; Steck, M.; Seifert, K. *Eur. J. Org. Chem.* **2000**, 1609–1615.
49. Saravanan, P.; Chandrasekhar, M.; Vijaya-Anand, R.; Singh, V. K. *Tetrahedron Lett.* **1998**, *39*, 3091–3092.
50. Corey, E. J.; Winter, R. A. E. *J. Am. Chem. Soc.* **1963**, *85*, 2677.
51. Corey, E. J.; Carey, F. A.; Winter, R. A. E. *J. Am. Chem. Soc.* **1965**, *87*, 934.
52. Hanessian, S.; Bargiotti, A.; LaRue, M. *Tetrahedron Lett.* **1978**, 737–740.
53. Appel, H. H.; Brooks, C. J. V.; Overton, K. H. *J. Chem. Soc.* **1959**, 3322.