Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 7, pp. 1229-1232, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00172-3

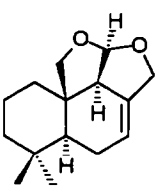
Determination of the Absolute Configuration of a Tetracyclic Drimane Sesquiterpenoid by Mosher's Method

Robert Velten[a], Wolfgang Steglich[a,*] and Timm Anke[b]

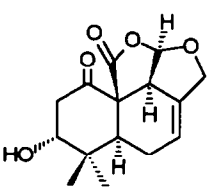
[a] Institut für Organische Chemie der Ludwig-Maximilians-Universität, Karlstraße 23, D-80333 München, Germany
[b] Lehrbereich Biotechnologie der Universität, Paul-Ehrlich-Str. 23, D-67663 Kaiserslautern, Germany

Abstract: The high field NMR application of the Mosher method has been successfully applied to determine the absolute configuration of a tetracyclic dihydroxydrimane derivative. The result indicates that highly functionalized drimanes from basidiomycetes correspond in their stereochemistry to (−)-drimenol.

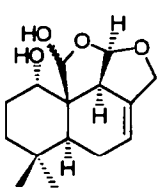
Tetracyclic drimane sesquiterpenoids with a dioxacyclooctane moiety are characteristic metabolites of several basidiomycetes. Ayer et al.[1,2] obtained marasmene (1) and some closely related derivatives, e. g. marasmone (2) and 1α,15-dihydroxymarasmene (3), from cultures of *Marasmius oreades*. 3 is also produced by a Canadian *Mniopetalum* species in addition to mniopetal A (4) and allied compounds which are potent inhibitors of reverse transcriptases[3,4]. A drimane derivative 5 with similar biological activity has recently been isolated from cultures of a Tasmanian *Kuehneromyces* species[5].



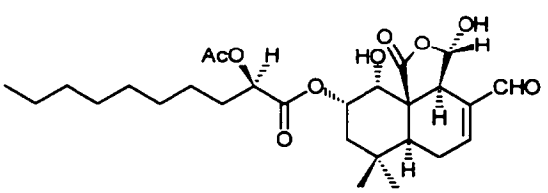
1



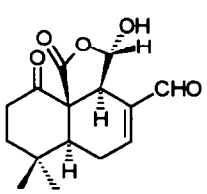
2



3



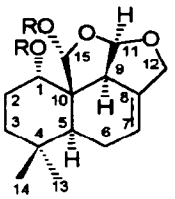
4



5

The absolute stereochemistry of these highly functionalized drimanes has not yet been determined. We chose the high field NMR modification of Mosher's method[6,7] for this purpose and applied it to (+)-1α,15-dihydroxymarasmene (**3**)[8] which occurs as a mixture of its C-15 epimers.

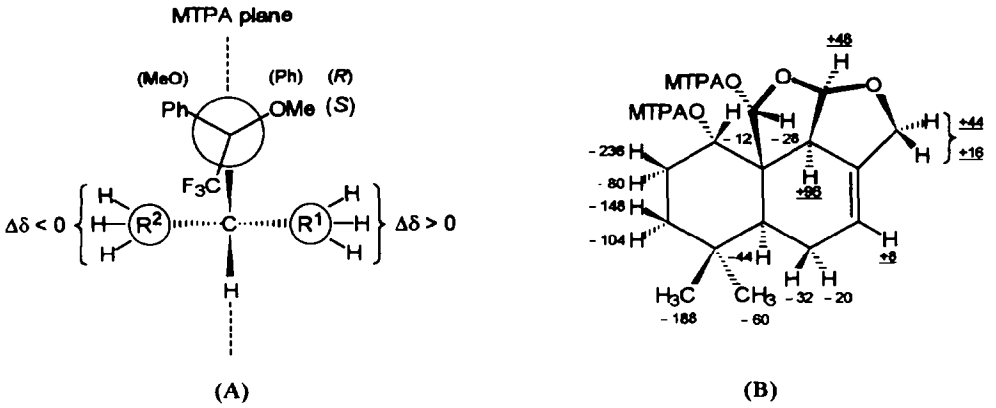
Treatment of **3** with both (*R*)-(−)- and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) in the presence of 4-(dimethylamino)pyridine (DMAP) yielded the (*S*)- and (*R*)-di-MTPA esters **6a** and **6b**, respectively. In each case only the C-15 *exo* epimer was formed.



6a, R = (*S*)-MTPA
6b, R = (*R*)-MTPA

Table 1. ^{1}H NMR data of (*S*)- and (*R*)-di-MTPA esters **6a** and **6b**, respectively (400 MHz; δ values in ppm; in $CDCl_3$); Δδ = δ(**6a**) − δ(**6b**) (Δδ values in Hz).

	6a			**6b**			
	δ [ppm]		*J* [Hz]	δ [ppm]		*J* [Hz]	Δδ [Hz]
1-H	5.23	dd	2.5/2.5	5.26	dd	2.5/2.5	−12
2α-H	1.45	dddd	15.0/3.0/3.0/2.5	1.65	dddd	15.0/3.0/3.0/2.5	−80
2β-H	1.40	dddd	15.5/15.0/4.0/2.5	1.99	dddd	15.0/14.8/4.0/2.5	−236
3α-H	1.15	ddd	15.5/13.0/3.0	1.41	ddd	14.8/13.0/3.7	−104
3β-H	0.81	ddd	13.0/4.0/3.0	1.18	ddd	13.0/3.7/3.0	−148
5-H	1.76	dd	11.5/6.2	1.87	dd	11.5/6.2	−44
6α-H	2.27	dm	18.5	2.32	dm	18.5	−20
6β-H	2.02	ddm	18.5/11.5	2.10	ddm	18.5/11.5	−32
7-H	5.71	s, br		5.69	s, br		+8
9-H	2.57	s, br		2.33	s, br		+96
11-H	5.60	d	3.6	5.48	d	3.6	+48
12-H	4.25	d, br	11.0	4.14	d, br	11.0	+44
	4.35	d, br	11.0	4.31	d, br	11.0	+16
13-H	0.73	s		0.88	s		−60
14-H	0.19	s		0.66	s		−188
15-H	6.13	s		6.20	s		−28



(A) (B)

Figure 1. (A) Model to determine the absolute configurations of MTPA derivatives[6]. (B) Δδ values obtained for the MTPA esters of (+)-1α,15-dihydroxymarasmene (**3**). Δδ values in Hz (400 MHz).

^{1}H NMR analysis of each diester and placing all protons with Δδ > 0 on the right side of the MTPA planes and those with Δδ < O on the left side as shown in Fig. 1[6,7] leads to the *S*-configuration at C-1 and C-15 of (+)-1α,15-dihydroxymarasmene (**3**). Molecular models indicate that both MTPA residues exert a cooperative anisotropic effect in the diesters **6a** and **6b**, the MTPA residue at C-15 having a major influence on the protons at rings A and C. Due to the effect of both MTPA residues, the observed chemical shift differences are much higher than in the examples given in the literature[6,7].

The absolute configuration of (+)-1α,15-dihydroxymarasmene (**3**) corresponds to that of (−)-drimenol[9] and other drimane derivatives from higher plants, liverworts and fungi[10]. Since the remaining drimanes from *Marasmius oreades* and *Mniopetalum* sp. are biogenetically closely related to **3** the same stereochemistry can be proposed for these compounds. In the case of (−)-11,12-dihydroxydrimene[4] from *Mniopetalum* sp. this has been proved by total synthesis[11].

Experimental: Spectral data were recorded on the following instruments: ^{1}H and ^{13}C NMR, Bruker AC-200 and AM-400; EI-MS, A.E.I. MS-50; IR, Perkin-Elmer 1420; UV, Varian Cary 17; CD, Jobin Yvon CNRS Roussel-Jouan Dichrographe III. Optical rotations were recorded with a Perkin Elmer 241 polarimeter. The mp's were determined with a Reichert hot-plate microscope and are uncorrected. Merck silica gel 60 (230–400 mesh) was used for flash chromatography. TLC was carried out on aluminium foils coated with silica gel Merck 60 F_{254}. All solvents were distilled prior to use.

Preparation of (*S*)- and (*R*)-MTPA Ester 6a and 6b: To a solution of **3** (13.5 mg) in CH_2Cl_2 (2.5 ml) were added successively DMAP (50 mg), NEt_3 (20 µl), and a solution of (*R*)-(−)- [or (*S*)-(+)-] MTPA-Cl (50 mg) in CH_2Cl_2 (1 ml). After stirring at 20 °C for 16 hours, the reaction mixture was diluted with Et_2O (40 ml) and washed consecutively with saturated aqueous NH_4Cl (2 x 30 ml), saturated aqueous $NaHCO_3$ (2 x 30 ml), and brine (2 x 30 ml). The organic phase was dried (Na_2SO_4) and evaporated to give an oil, which was chromatographed on a silica gel column. Elution with petroleum ether$_{40-60}$ – EtOAc (10:1) gave (*S*)-MTPA-ester **6a** (12.4 mg) or (*R*)-MTPA-ester **6b** (8.5 mg), respectively. (*S*)-MTPA-ester **6a**: colorless oil; R_f 0.56 (petroleum

ether$_{40-60}$ – EtOAc, 5:1); $[\alpha]_D^{20}$ +13 (*c* 0.60, $CHCl_3$); UV λ_{max}^{MeCN} nm (ε_{rel}) 208 (sh, 1), 256 (0.07); IR (KBr) cm^{-1} 2940, 1755, 1446, 1271, 1238, 1171, 1124, 1083, 1037, 996, 944, 865, 725; ^1H NMR, Table 1; HREI-MS (70 eV; DI 180 °C) *m/z* (relative intensity %) 698.2318 (12, M^+, calcd for $C_{35}H_{36}O_8F_6$ 698.2315), 466 (51), 465 (92), 464 (40), 232 (41), 231 (89), 203 (80), 202 (59), 201 (60), 190 (43), 189 (100), 173 (50), 105 (78). (*R*)-MTPA-ester **6b**: colorless oil; R_f 0.45 (petroleum ether$_{40-60}$ – EtOAc, 5:1); $[\alpha]_D^{20}$ +72 (*c* 0.40, $CHCl_3$); UV λ_{max}^{MeCN} nm (ε_{rel}) 208 (sh, 1), 258 (sh, 0.09); IR (KBr) cm^{-1} 2940, 1745, 1450, 1271, 1246, 1215, 1167, 1116, 1077, 1031, 1015, 990, 859, 720; ^1H NMR, Table 1; HREI-MS (70 eV; DI 180 °C) *m/z* (relative intensity %) 698.2317 (2, M^+, calcd for $C_{35}H_{36}O_8F_6$ 698.2315), 465 (89), 464 (39), 231 (87), 203 (71), 202 (55), 201 (82), 189 (100).

Acknowledgement: We thank the Deutsche Forschungsgemeinschaft for financial support of this work.

References and Notes

1. W. A. Ayer, P. A. Craw, T. J. Stout and J. Clardy, *Can. J. Chem.* **1989**, *67*, 773.
2. W. A. Ayer, and P. A. Craw, *Can. J. Chem.* **1989**, *67*, 1371.
3. A. Kuschel, T. Anke, R. Velten, D. Klostermeyer, W. Steglich and B. König, *J. Antibiot.*, submitted.
4. R. Velten, D. Klostermeyer, B. Steffan, W. Steglich, A. Kuschel and T. Anke, *J. Antibiot.*, submitted.
5. G. Erkel, K. Lorenzen, T. Anke, R. Velten, A. Gimenez and W. Steglich, *Z. Naturforsch., Part C*, submitted.
6. I. Ohtani, T. Kusumi, M. O. Ishitsuka and H. Kakisawa, *Tetrahedron Lett.* **1989**, *30*, 3147.
7. I. Ohtani, T. Kusumi, M. Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092. For further applications of this method compare e. g.: M. D. Preite, J. Zinczuc, M. I. Colombo, J. A. Bacigaluppo, M. Gonzáles-Sierra and E. A. Rúveda, *Tetrahedron: Asymmetry* **1993**, *4*, 17; G. Cimino, A. Crispino, R. de A. Epifanio, A. Madaio, C. A. Mattia, L. Mazzarella, R. Puliti, E. Trivellone and M. Uriz, *Tetrahedron* **1992**, *48*, 9013; S. V. Ley, H. Lovell and D. J. Williams, *J. Chem. Soc., Chem. Commun.* **1992**, 1304.
8. In ref. 2 the optical rotation of **3** is not given. We have therefore oxidized (+)-**3** from *Mniopetalum* sp. with pyridinium dichromate to (+)-marasmen-1,15-dione which exhibited the same m.p. and sign of optical rotation as the dione obtained by oxidation of 1α,15-dihydroxymarasmene from *Marasmius oreades* (ref. 2). The negative sign of $[\theta]_{299}$ in the CD spectrum of (+)-marasmen-1,15-dione given in ref. 2 should be corrected to positive.
9. H. H. Appel, C. J. W. Brooks, and K. H. Overton, *J. Chem. Soc.* **1959**, 3322.
10. B. J. M. Jansen and A. de Groot, *Nat. Prod. Rep.* **1991**, *8*, 309.
11. K. Mori and H. Watanabe, *Tetrahedron* **1986**, *42*, 273.

(*Received in UK* 23 *May* 1994)