UV max (MeOH) 321 nm (ε 5700), 310 (6770), 277 (20 600), min 266 (18 400); ^{1}H NMR ($CDCl_3$) δ 9.41 (1 H, s), 8.89 (1H, s), 3.87 (6 H, s).

Strategy and relevant data of the synthesis of the two heptamers AMUAMGA and AUUUAMC are presented in Table I.

Preparation of 5′-OH-ACUACGA-2′,3′-OH. Fully protected heptamer AMUAMGA (20 mg) was dissolved in a solution of 20% aqueous ammonia (1 mL) and dioxane (3 mL). After 8 h, the solvent was evaporated in vacuo. The residue was dissolved in 20% aqueous ammonia (2 mL) and pyridine (4 mL). After 4 days at 37 °C, the solvent was evaporated. The residue was washed with anhydrous ether and was treated at 20 °C for 15 min with acetic acid–water (4:1 v/v).[19] After evaporation of the solvent, the residue was washed with anhydrous ether and was treated with 1 M tetrabutylammonium fluoride in tetrahydrofuran (0.7 mL) for 3 h. After evaporation of solvent, the residue was dissolved in water (30 mL) and was filtered through a short column of [(diethylamino)ethyl]cellulose.[22] The column was then eluted by 1 M triethylammonium bicarbonate buffer (pH 7.2). Evaporation of the eluant yielded the unprotected heptamer ACUACGA. Further purification by TLC on poly(ethylenimine) afforded the heptamer (7 mg, approximately 70%) as an amorphous compound.[7]

Preparation of 5′-OH-AUUUACC-2′,3′-OH. Fully protected heptamer AUUUAMC (10 mg) was deprotected by the same procedure as in the preparation of ACUACGA. The resulting heptamer 5′-OH-AUUUACC-2′,3′-OH was isolated as an amorphous compound (4 mg, approximate yield 70%).

Preparation of 5′-OH-AUUUAUC-2′,3′-OH. Fully protected heptamer AUUUAMC (7 mg) was dissolved in a solution of N^1,N^1,N^3,N^3-tetramethylguanidinium *syn*-2-pyridinealdoximate (3.8 mg) in dioxane (1 mL) and water (0.1 mL). After 7 h, the solvent was evaporated to yield a residue which was dissolved in 20% aqueous ammonia (2 mL) and pyridine (4 mL). After 3 days at 37 °C, the solvent was evaporated, and the residue was washed with ethyl ether. Subsequent detritylation and then desilylation were similar to those described in the preparation of 5′-OH-ACUACGA-2′,3′-OH. Heptamer 5′-OH-AUUUAUC-2′,3′-OH was obtained as an amorphous compound (3 mg, approximate yield 70%).

***p*-Chlorophenyl Ester of 5′-*O*-(Dimethoxytrityl)-2′-*O*-(*tert*-butyldimethylsilyl)-N^4,N^4-dimethylcytidylyl-(3′→5′)-2′,3′-*O*-bis(*tert*-butyldimethylsilyl)-N^4-benzoylcytidine (24).** A solution of dinucleotide **23** (150 mg, 0.10 mmol) and 40% aqueous dimethylamine (2 mL) in dioxane (4 mL) was stirred for 5 min. Removal of the solvent yielded a residue which was purified by chromatography on silica gel to give **24**: 115 mg (81%); UV max (MeOH) 278 nm (ε 24 800), 262 (18 000), min 255 (15 900); ^{1}H NMR ($CDCl_3$) δ 3.80 (6 H, s), 3.11 (6 H, br s).

Acknowledgment. I thank Diana M. Schmidt for technical assistance.

Registry No. **11**, 82444-76-6; **12**, 82456-20-0; **13**, 82444-77-7; **14**, 82444-78-8; **15**, 82444-79-9; **16**, 82456-21-1; **17**, 82444-80-2; **18**, 72409-47-3; **19**, 82444-81-3; *M* (**20**), 82444-82-4; *M* (**20**) phosphorodiester salt, 82444-85-7; **21**, 81246-80-2; **22**, 81265-94-3; **23**, 82444-83-5; **24**, 82444-84-6; 5′-OH-ACUACGA-2′,3′-OH, 82444-86-8; [$(MeO)_2$Tr]bzA±*M*±U±bzA±*M*±IsoG±bzA-$(OSi)_2$, 82494-74-4; 5′-OH-AUUUACC-2′,3′-OH, 82444-87-9; [$(MeO)_2$Tr]bzA±U±U±U±bzA±*M*±bzC-$(OSi)_2$, 82494-73-3; 5′-OH-AUUUAUC-2′,3′-OH, 82444-88-0; [$(MeO)_2$Tr]U±bzA-ClPh, 82468-98-2; [$(MeO)_2$Tr]bzA±U±U-ClPh, 82444-89-1; *M*±bzC-$(OSi)_2$, 82456-22-2; U±bzA±*M*±bzC-$(OSi)_2$, 82456-23-3; [$(MeO)_2$Tr]Uβ-bzA±*M*±bzC-$(OSi)_2$, 82456-24-4; [$(MeO)_2$Tr]bzA-ClPh, 82456-25-5; [$(MeO)_2$Tr]bzA±*M*-ClPh, 82444-90-4; [$(MeO)_2$Tr]bzA±*M*±U-ClPh, 82444-91-5; *M*±CE, 82444-92-6; U±CE, 82444-93-7; IsoG±bzA-$(OSi)_2$, 82444-94-8; bzA±*M*±IsoG±bzA-$(OSi)_2$, 82456-26-6; [$(MeO)_2$Tr]bzA±*M*±CE, 82444-95-9; [$(MeO)_2$Tr]bzA±*M*±U±CE, 82444-96-0; [$(MeO)_2$Tr]bzA±*M*±IsoG±bzA-$(OSi)_2$, 82468-99-3; *p*-Chlorophenyl phosphodichloridate, 772-79-2; 1,2,4-triazole, 288-88-0; 5′-*O*-(dimethoxytrityl)-2′,3′-*O*-bis(*tert*-butyldimethylsilyl)-N^4-benzoylcytidine, 81246-77-7; methylamine, 74-89-5; dimethylamine, 124-40-3; hydrazine, 302-01-2; 2′,3′-*O*-bis(*tert*-butyldimethylsilyl)-N^4-benzoylcytidine, 72409-40-6.

(22) J. Imai and P. F. Torrence, *J. Org. Chem.*, **46**, 4015 (1981).

Isolation and Structural Identification of 8(14),15-Sandaracopimaradiene-7α,18-diol from *Iboza riparia*

Norbert De Kimpe*[1] and Niceas Schamp

Laboratory of Organic Chemistry, Faculty of Agricultural Sciences, State University of Gent, Coupure Links 653, B-9000 Gent, Belgium

Luc Van Puyvelde,* Serge Dubé, and Monique Chagnon-Dubé

Centre Universitaire de Recherche sur la Pharmacopée et la Médicine Traditionelle, Curphametra, B.P. 52, Butare, Rwanda

Francois Borremans and Marc J. O. Anteunis

Laboratory of Organic Chemistry, NMR Spectroscopic Unit, Faculty of Sciences, State University of Gent, Krijgslaan 271 (S4), B-9000 Gent, Belgium

Jean-Pierre Declercq,[1] Gabriel Germain, and Maurice Van Meerssche

Laboratoire de Chimie Physique et de Cristallographie, Bâtiment Lavoisier, B-1348 Louvain-la-Neuve, Belgium

Received December 29, 1981

The isolation from *Iboza riparia* and structural elucidation of 8(14),15-sandaracopimaradiene-7α,18-diol, a novel diterpene diol with interesting pharmaceutical properties, are described.

Iboza riparia (Hochst) N.E.Br. (Labiatae) is an important medicinal plant in Rwanda (Central Africa) and is commonly used by the native people.[2] Some constituents of the leaves have been described recently, including

0022-3263/82/1947-3628$01.25/0

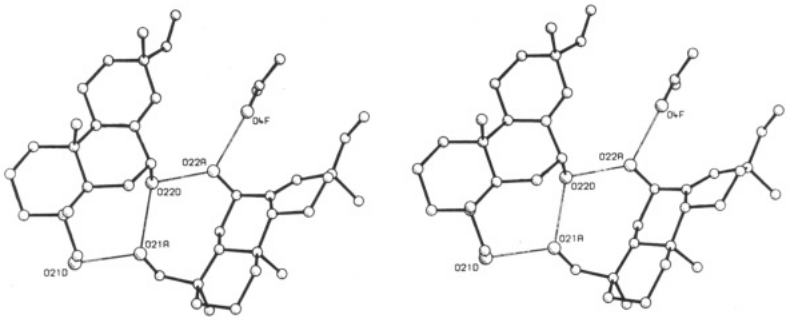
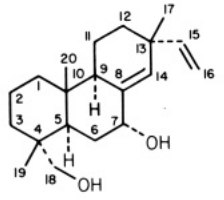


Figure 1. Stereoscopic view of two molecules of compound 1 linked together and to one molecule of acetone by hydrogen bonding.

ibozol,[3] 7α-hydroxyroyleanone,[3] and some 6-substituted α-pyrones.[4,5] Our screening for biological active fractions of the extract of leaves of *I. riparia* led to the isolation of a novel diterpene diol, i.e., 8(14),15-sandaracopimaradiene-7α,18-diol (1), which displayed significant



1

antimicrobial and antispasmodic properties. Compound 1 ($C_{20}H_{32}O_2$) was isolated in 0.9% yield from the chloroform extract of the leaves of *I. riparia* and was purified by chromatography on a silica gel column in benzene (C_6H_6–$CHCl_3$–MeOH gradient). The fractions eluted with $CHCl_3$–MeOH (97:3) gave, after crystallization from benzene, colorless crystals (mp 86–87 °C). The optical rotation was measured in methanol (11.9 mg of sample in 2 mL) and gave the following values for [α]: −87.1° (589 nm), 90.8° (578 nm), −103.9° (546 nm), −189.4° (436 nm), −324.4° (365 nm). The IR spectrum displayed hydroxyl absorption (3350 cm^{-1}), while the mass spectrum showed a molecular ion (m/e 304) and a fragment ion corresponding to loss of water (m/e 296).

The 360-MHz ^1H NMR spectrum (C_6D_6) showed three three-proton singlets at δ 0.66, 0.73, and 1.04, indicating three methyl groups at a quaternary carbon. The olefinic resonances at δ 5.83 (1 H, dd, J = 10.6, 17.4 Hz), 5.04 (1 H, dd, J = 1.4, 17.4 Hz), and 5.00 (1 H, dd, J = 1.4, 10.6 Hz) are attributed to a vinyl group carried by a quaternary carbon. Another olefinic proton is situated at δ 5.45 (1 H, d, J = 1.95 Hz). The characteristic AX system at δ 3.63 and 2.99 (each 1 H, J = 11.6 Hz) points to a hydroxymethyl substituent linked to a quaternary carbon, while another oxygen-substituted methine proton is located at δ 4.11 (1 H, $J \approx 2.3$, 3.1 Hz, $\sum J$ = 5.4 Hz). These characteristic data led to the proposal of a diterpene diol of the pimaradiene type.[6] The 50-MHz ^{13}C NMR spectrum lends support to a pimaradiene skeleton because of the remarkable similarity between the spectrum of the title compound and ^{13}C NMR data reported in a systematic analysis of diterpenic compounds.[7,11b] This comparison permitted the determination of the stereochemistry at C-13 and the localization of the olefinic double bond at the C(8)–C(14) position.[7a] The ^{13}C NMR (C_6D_6) data are as follows: δ 148.8 (d, C-15), 140.0 (s, C-8), 133.7 (d, C-14), 110.8 (t, C-16), 73.4 (s, C-7), 70.6 (t, C-18), 46.4 (d, C-9), 39.5 (d, C-5), 38.8 (t, C-1), 38.4 (s, C-10), 37.9 (s, C-4), 37.6 (s, C-13), 35.3 (t, C-3), 34.6 (t, C-12), 28.8 (t, C-6), 25.9 (q, C-17), 18.6 (2t, C-2 and C-11), 18.3 (q, C-19), 14.9 (q, C-20). Corrlelation with ^1H NMR assignment were performed by using residual splittings measured in a series of SFORD experiments. Additionally, double-irradiation measurements (^1H NMR) confirmed the proposed structural elucidation. Further evidence for the C-18 stereochemistry was obtained by comparison of the average chemical shift value of the hydroxymethyl protons of 1 with ^1H NMR data reported for a large number of diterpenes.[8] Only the position and stereochemistry of the second hydroxyl function remained to be determined. Comparison of our spectral data with those of certian hydroxylated diterpenediols[9-12] clearly excluded substitution in the A ring. Moreover, double-resonance experiments indicated that the 7-position was hydroxylated.

The ^{13}C chemical shifts of 8(14),15-sandaracopimaradien-18-ol[7a,11b] fitted extremely well with the data of compound 1 except for the C-5, C-6, C-7, C-8, C-9, and C-14 carbons. The determination of the C-7 stereochemistry originated from the large γ-shielding effects (^{13}C NMR) at C-5 and C-9, which prove the axial character. The deshielding effects at C-6 and C-8 support this attribution. If implantation of the hydroxyl function were at the 6-position (equatorial or axial), upfield shifts of several parts per million would be observed at C-4 and C-10, in contrast to experimental observations. On the other hand, the well-established shift increments (^{13}C NMR) for a hydroxyl substituent[13] unequivocally allow a

(1) N. De Kimpe and J. P. Declercq are "Research Associates" of the Belgian National Fund for Scientific Research.

(2) J. M. Watt and M. G. Breyer-Brandwijk, "The Medicinal and Poisonous Plants of Southern and Eastern Africa", E. and S. Livingstone, Edingburgh, South Africa, 1980, p 516; L. Van Puyvelde and A. Kayonga, *Afr. Med.*, 14, 925 (1975); L. Van Puyvelde, *Rapp. Deuxième Colloq. CAMES*, 60 (1976).

(3) R. Zelnik, E. Rabenhorst, A. K Matida, H. E. Gottlieb, D. Lavie, S. Panizza, *Phytochemistry*, 17, 1795 (1978).

(4) L. Van Puyvelde, S. Dubé, E. Uwimana, C. Uwera, R. A. Domisse, E. L. Esmans, O. Van Schoor, and A. J. Vlietinck, *Phytochemistry*, 18, 1215 (1979).

(5) L. Van. Puyvelde, N. De Kimpe, S. Dubé, M. Chagnon-Dubé, Y. Boily, F. Borremans, N. Schamp, and M. J. O. and Anteunis, *Phytochemistry*, 20, 2753 (1981).

(6) E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, P. W. Jeffs, and J. D. McChesney, *J. Org. Chem.*, 30, 713 (1965).

(7) (a) E. Wenkert and B. L. Buckwalter, *J. Am. Chem. Soc.*, 94, 4367 (1972); (b) J. Polonsky, Z. Baskevitch, N. Cagnoli-Bellavita, P. Ceccherelli, B. L. Buckwalter, and E. Wenkert, *J. Am. Chem. Soc.*, 94, 4369 (1972).

(8) A. Gaudemer, J. Polonsky, and E. Wenkert, *Bull Soc. Chim. Fr.*, 407 (1964).

(9) R. C. Cambie, I. R. Burfitt, T. E. Goodwin, and E. Wenkert, *J. Org. Chem.*, 40, 3789 (1975).

(10) R. A. Laidlaw and J. W. W. Morgan, *J. Chem. Soc.*, 644 (1963).

(11) (a) R. R. Jefferies and T. Ratajczak, *Aust. J. Chem.*, 26, 173 (1973); (b) R. C. Cambie, R. J. Madden, and J. C. Parnell, *Aust. J. Chem.*, 24, 217 (1971); (c) P. K. Grant, M. H. G. Munro, *Tetrahedron Lett.*, 3729 (1965); (d) P. S. Rao, G. P. Sachdev, T. R. Seshadri, and H. B. Singh, *Tetrahedron Lett.*, 4685 (1968); (e) J. Polonsky, Z. Baskevich, N. C. Bellavita, and P. Ceccherelli, *Bull. Soc. Chim. Fr.*, 1912 (1970).

(12) F. Bohlman, M. Lonitz, *Chem. Ber.*, 111, 843 (1978).

similar conclusion. X-ray crystallographic analysis of diterpenediol 1 confirmed the proposed structure. When the title compound was recrystallized from acetone, one solvent molecule was incorporated per two diterpene diol molecules (mp 76–81 °C). The X-ray analysis of the latter revealed that two molecules of compound 1 are arranged together by hydrogen bonds between both of the 7α-hydroxyl groups and both of the hydroxymethyl groups. Each time, such a dimeric entity is linked to the acetone carbonyl by one 7α-hydroxyl function (Figure 1). The structure was solved by YZARC[16] and refined by the SHELX 76 program[17] on the basis of 2918 reflections selected from 6241 measured reflections and for which $I > 2.5\ \sigma(I)$. The incident radiation was Mo Kα (λ = 0.7107 Å). The final R value was 0.139. Crystal data: $C_{20}H_{32}O_2 \cdot 0.5CH_3COCH_3$; monoclinic; space group $P2_1$; cell dimensions a = 14.167 (5) Å, b = 22.721 (14) Å, c = 12.965 (5) Å, β = 101.32 (3)°; V = 4092.1 (32) Å^3; Z = 8. Atomic coordinates and equivalent isotropic temperature factors, interatomic distances, and bond angles are included in the supplementary material. Among natural substances of the pimaradienediol, isopimaradienediol, or sandaracopimaradienediol type, the title product is the only one containing OH functions at the 7,18-positions instead of the more common 2,18-,[9] 3,18-,[10] or 3,19-diol[11] combinations. The 7-position in these types of natural products is rarely hydroxylated. Some 7α-hydroxylated 8(14),15-sandaracopimaradienes, including 8(14),15-sandaracopimaradiene-1β,7α-diol and 8(14),15-sandaracopimaradiene-7α-ol, were isolated from *Zexmenia* species.[12] Recently however, the corresponding methyl ester analogue of 1, methyl 7α-hydroxysandaracopimarate, was isolated from *Juniperus communis*[14] and was also obtained by photooxidation of methyl isopimarate.[15]

Acknowledgment. We are indebted to the Université Nationale du Rwanda and to the Belgian National Fund for Scientific Research for Financial support. We are grateful to Dr. J. Polonsky (CNRS, Gif-sur-Yvette, France) for helpful discussions.

Registry No. 1, 82190-51-0.

Supplementary Material Available: Tables containing atomic coordinates and equivalent isotropic temperature factors, interatomic distances, and bond angles (5 pages). Ordering information is given on any current masthead page.

(13) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Am. Chem. Soc.*, **92**, 1138 (1970).
(14) J. de Pascual Teresa, A. F. Barrero, L. Muriel, A. San Feliciano, and M. Grande, Phytochemistry, **19**, 1153 (1980).
(15) J. L. Fourrey, J. Rondest, and J. Polonsky, *Tetrahedron*, **26**, 3839 (1970).
(16) J. P. Declercq, G, Germain, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **A35**, 622 (1979).
(17) G. M. Sheldrick, "SHELX 76, Program for Crystal Structure Determination", University of Cambridge, Cambridge England.

Palladium-Catalyzed Carbonylation of Vinyl Halides: A Route to the Synthesis of α-Methylene Lactones

Larry D. Martin and J. K. Stille*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received January 18, 1982

α-Methylene γ-lactones were synthesized in high yields by the palladium-catalyzed carbonylation reactions of alkyl-substituted 3-bromobut-3-en-1-ols under mild conditions. The bromo alcohols were obtained by the reaction of [1-(trimethylsilyl)vinyl]magnesium bromide with various epoxides followed by conversion of the trimethylsilyl group to bromide. By starting with optically active epoxides such as (*R*)-1,2-epoxypropane or (2*R*,3*R*)-2,3-epoxybutane, the corresponding lactones could be obtained virtually optically pure. The carbonylation reaction is selective in that it generates only γ-lactones when there is a choice of two vinylic iodides or two alcohols that could lead either to the five- or six-membered rings.

Introduction

As a consequence of the wide range of biological activity, particularly the cytotoxic and antitumor activity,[1] fungitoxicity,[2] and plant growth inhibition[3] possessed by α-methylene-γ-butyrolactones, this class of compounds has been the object of considerable synthetic activity.[4] The transition metal assisted syntheses of unsaturated lactones have been developed more recently, some of the most useful transformations depending on carbonylation reactions. Many of the carbonylation reactions leading to γ-lactones are stoichiometric; the synthesis of a wide variety of butenolides, for example, requiring molar quantities of sodium tetracarbonylcobaltate[5] or dicobalt octacarbonyl,[6] although moderate turnovers have been realized with these cobalt carbonyls.[5,7] Stoichiometric or greater quantities of nickel tetracarbonyl are required to convert homopropargyl alcohols (**3**)[8] or alcoholic vinyl bromides (**1**)[9] to the corresponding α-methylene γ-lactones (**2**). More

(1) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*, 1147.
(2) (a) Hutchinson, C. R. *J. Org. Chem.* **1974**, *39*, 1854. (b) Bergman, B. H. H.; Berjeisbergen, J. C. M.; Overeem, J. C.; Kaars Sijpesteijn, A. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 709.
(3) Iino, Y.; Tanako, A.; Yamashita, K. *Agric. Biol. Chem.* **1972**, *36*, 2505.
(4) For a review of classical synthetic organic methods applied to α-methylene-γ-butyrolactone, see Grieco, P. A. *Synthesis* **1975**, 67.
(5) Heck, R. F. *J. Am. Chem. Soc.* **1963**, *85*, 1460; *Ibid.* **1964**, *86*, 2819.
(6) Nienburg, H.; Ellschnig, G. German Patent 1 066 572, 1959.
(7) Alper, H.; Currie, J. K.; Des Abbayes, H. *J. Chem. Soc., Chem. Commun.* **1978**, 311.
(8) (a) Jones, E. R. H.; Shen, T. Y.; Whiting, M. C. *J. Chem. Soc.* **1950**, 230. (b) Jones, E. R. H.; Whitham, G. H.; Whiting, M. C. *Ibid.* **1957**, 4628.
(9) Matsuda, I. *Chem. Lett.* **1978**, 773.

0022-3263/82/1947-3630$01.25/0