

TOTAL SYNTHESSES OF (±)-ISOAGATHOLACTONE AND (±)-12α-HYDROXYSPONGIA-
13(16),14-DIEN

Tatsuhiko Nakano* and María Isabel Hernández

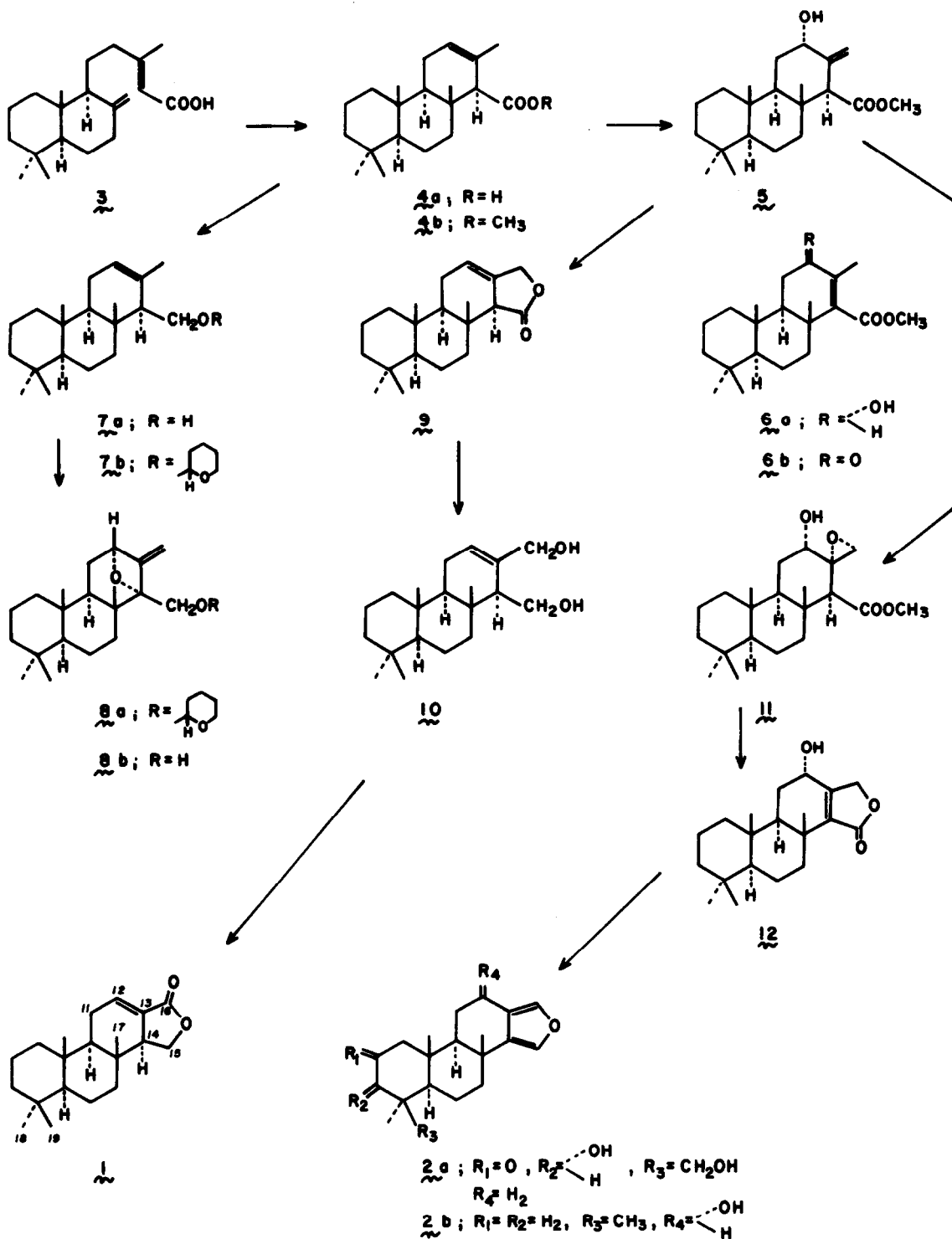
Centro de Química, Instituto Venezolano de Investigaciones Científicas
(I.V.I.C.), Apartado 1827, Caracas 1010-A, Venezuela

Abstract - (±)-Isoagatholactone 1 and (±)-12α-hydroxyspongia-13(16),14-dien 2b, a fundamental skeleton of spongiadiol 2a and its congeners, have been synthesized from (±)-labda-8(20),13-dien-15-oic acid 3.

Among a large number of interesting metabolites¹ produced by the sponges of the orders Dictyoceratida and Dendroceratida, the spiculeless horny sponges, isoagatholactone 1² and spongiadiol 2a and its congeners^{3a,b} are the only natural substances with this new diterpenoid system. We report herein the total synthesis of (±)-isoagatholactone 1 and (±)-12α-hydroxyspongia-13(16),14-dien 2b,^{3c} a fundamental skeleton of spongiadiol 2a and its related furanoid diterpenes.

(±)-Labda-8(20),13-dien-15-oic acid 3^{4a,b} was chosen as the starting material. On refluxing with 88% formic acid for 4 hr it provided a single cyclized isomer 4a^{4a} in 70% yield which on methylation with ethereal diazomethane led to 4b, m.p. 75-80°, $\underline{m/e}$ 318 (M^+), ν_{\max} (KBr) 1720 cm^{-1} (COOCH_3), δ (CDCl_3) 0.83, 0.86, 0.90, 0.95 (3H, s, CH_3), 1.60 (3H, s, CH_3 -16), 2.93 (1H, m, H-14), and 3.66 (3H, s, OCH_3). Photooxygenation⁵ of 4b in pyridine in the presence of hematoporphyrin at 20° for 72 hr gave the allylic alcohols 5 (25%), m.p. 183-185°, $\underline{m/e}$ 334 (M^+), ν_{\max} (KBr) 3550 (OH), 1725 (COOCH_3), and 1655 cm^{-1} (terminal C=C), δ (CDCl_3) 0.80 (3H, s, CH_3), 0.86 (6H, s, 2CH_3), 1.01 (3H, s, CH_3), 3.33 (1H, s, H-14), 3.63 (3H, s, OCH_3), 4.36 (1H, m, H-12), 4.83 (1H, m, H-16), and 5.03 (1H, m, H-16) and 6a (44%), m.p. 146-148°, $\underline{m/e}$ 334 (M^+), ν_{\max} (KBr) 3470 (OH) and 1692 cm^{-1} (α,β -unsaturated ester), δ (CDCl_3) 0.80, 0.83, 0.86 (3H, s, CH_3), 1.16 (3H, s, CH_3 -17), 1.73 (3H, s, CH_3 -16), 3.73 (3H, s, OCH_3), and 4.00 (1H, t, H-12), and the α,β -unsaturated ketone 6b (8%), m.p. 104-106°, $\underline{m/e}$ 332 (M^+), ν_{\max} (KBr) 1730 (COOCH_3), 1675 (α,β -unsaturated CO), and 1630 cm^{-1} (conjugated C=C), whose structure was confirmed by preparing it from 6a by oxidation.

Reduction of 4b with lithium aluminum hydride afforded in 98% yield the alcohol 7a as a semisolid, $\underline{m/e}$ 290 (M^+), δ (CDCl_3) 0.81 (6H, s, 2CH_3), 0.84, 0.87 (3H, s, CH_3), 1.78 (3H, s, CH_3 -16), 3.90 (2H, m, CH_2OH), and 5.50 (1H, t,



H-12). 7a, after conversion to the tetrahydropyranyl ether 7b, was submitted to photooxygenation under the same conditions as above. Contrary to our expectation, however, it did not yield the diol corresponding to 5 but instead the cyclized ether 8a which after acid hydrolysis was identified as 8b, m.p. 197-200°, $\underline{m/e}$ 304 (M^+), ν_{\max} (KBr) 3430 cm^{-1} (OH), δ (CDCl_3) 0.79, 0.85 (6H each, s, 2CH_3), 3.76 (2H, ABq, \underline{J} 11 Hz, CH_2OH), 4.40 (1H, t, H-12), 5.06 (1H, s, H-16), and 5.20 (1H, s, H-16).

5 did not undergo an allylic rearrangement with 3.5% sulfuric acid in dioxane at room temperature. However, heating of 5 at refluxing temperature in the same acidic medium for 20 hr led in 83% yield to a lactone 9, m.p. 142°, $\underline{m/e}$ 302 (M^+), ν_{\max} (KBr) 1770 cm^{-1} (γ -lactone), δ (CDCl_3) 0.83 (6H, s, 2CH_3), 0.86, 0.89 (3H, s, CH_3), 2.73 (1H, s, H-14), 4.58 (2H, m, H-16) and 5.66 (1H, m, H-12). On reduction with lithium aluminum hydride 9 afforded in 95% yield the diol 10, m.p. 149-151°, $\underline{m/e}$ 306 (M^+), δ (CDCl_3) 0.73, 0.80 (3H, s, CH_3), 0.86 (6H, s, 2CH_3), 3.86 (2H, bm, CH_2OH -15), 4.16 (2H, ABq, \underline{J} 12 Hz, CH_2OH -16), and 5.76 (1H, m, H-12). Oxidation of 10 with Collins reagent⁶ in methylene chloride furnished in 59% yield (\pm)-isoagatholactone 1,⁷ m.p. 140-141°, $\underline{m/e}$ 302 (M^+ , 5%), 287 (11), 192 (100), 191 (49), 177 (77), and 137 (41), ν_{\max} (KBr) 1760 (α,β -unsaturated γ -lactone) and 1685 cm^{-1} (conjugated C=C), δ (CDCl_3) 0.75, 0.81, 0.86, 0.93 (3H, s, CH_3), 2.20 (2H, bm, H-11, H-11), 2.70 (1H, bm, H-14), 4.03 (1H, t, \underline{J} 9 Hz, H-15), 4.36 (1H, t, \underline{J} 9 Hz, H-15), and 6.86 (1H, q, \underline{J} 3 Hz, H-12). The IR, NMR, and mass spectral data of this synthetic material were identical with those² reported for (+)-isoagatholactone.

On epoxidation with m -chloroperbenzoic acid in methylene chloride 5 gave in 99% yield the α -epoxide 11, m.p. 196-198°, $\underline{m/e}$ 350 (M^+), ν_{\max} (KBr) 3480 (OH) and 1730 cm^{-1} (COOCH_3), δ (CDCl_3) 0.80 (3H, s, CH_3), 0.85 (6H, s, 2CH_3), 1.11 (3H, s, CH_3), 2.66 (1H, d, \underline{J} 5 Hz, H-16), 3.21 (1H, s, H-14), 3.50 (1H, d, \underline{J} 5 Hz, H-16 and 1H, m, H-12), and 3.58 (3H, s, OCH_3), which by the action of lithium diisopropylamide (tetrahydrofuran, $-70^\circ \rightarrow$ r. t.) for 3 hr underwent β -elimination and lactonization, providing in 50% yield the lactone 12, m.p. 263-265°, $\underline{m/e}$ 318 (M^+), ν_{\max} (KBr) 3370 (OH) and 1735 cm^{-1} (α,β -unsaturated γ -lactone), δ (CDCl_3) 0.83, 0.86, 0.90, 1.10 (3H, s, CH_3), 2.60 (1H, dm, \underline{J} 12 Hz, H-7 β), 4.42 (1H, m, H-12) and 4.70 (2H, ABq, \underline{J} 17 Hz, H-16, H-16). Reduction of 12 with diisobutylaluminum hydride⁸ in tetrahydrofuran afforded in 19% yield the furanoid 2b as an amorphous solid, $\underline{m/e}$ 302 (M^+), δ (CDCl_3) 0.83, 0.86, 0.90, 1.15 (3H, s, CH_3), 4.95 (1H, m, H-12), 7.06 (1H, d, \underline{J} 1 Hz, H-15 or H-16), and 7.36 (1H, d, \underline{J} 1 Hz, H-16 or H-15).

Acknowledgement - Part of this work has been supported by a research grant No. S1-1209 from the Consejo Nacional de Investigaciones Científicas y Tecnológicas (CONICIT), Caracas.

References and Notes

1. L. Minale, G. Cimino, S. de Stefano, and G. Sodano, Fortschr. Chem. Org. Naturst. 33, 1 (1976).
2. G. Cimino, D. de Rosa, S. de Stefano, and L. Minale, Tetrahedron 30, 645 (1974).
3. (a) R. Kazlauskas, P. T. Murphy, and R. J. Wells, Tetrahedron Letters 903 (1979); (b) R. Kazlauskas, P. T. Murphy, P. J. Wells, K. Noak, W. E. Oberh nsli, and P. Sch nholzer, Aust. J. Chem. 32, 867 (1979); (c) For the nomenclature of these compounds, see ref. 3b.
4. (a) T. Nakano and C. Djerassi, J. Org. Chem. 26, 167 (1961); G. Ohloff, Annalen 617, 134 (1958). We thank Mrs. V. De Santis de Molinaro and Dr. J. D. Medina for a kind gift of (\pm)-labda-8(20),13-dien-15-oic acid.
(b) C. W. L. Bevan, D. E. U. Ekong, and J. I. Okogun, J. Chem. Soc. C 1067 (1968); S. Borg, M. F tizon, and P. Laszlo, Bull. Soc. chim. Fr. 10, 2310 (1963).
5. G. O. Schenck, O.-A. Neum ller, and W. Eisfeld, Justus Liebig's Ann. Chem. 618, 202 (1958); A. K. Banerjee, A. Martin, and T. Nakano, J. Org. Chem. 38, 3807 (1973).
6. J. C. Collins, W. W. Hess, and F. J. Frank, Tetrahedron Letters 3363 (1968).
7. After we had completed our present work, a similar synthesis appeared [P. M. Imamura, M. Gonz lez Sierra, and E. A. R veda, J. Chem. Soc. Chem. Commun. 734 (1981)].
8. H. Minato and T. Nagasaki, J. Chem. Soc. C 377 (1966).

(Received in USA 18 November 1981)