This article was downloaded by: [NUS National University of Singapore] On: 27 June 2013, At: 23:21 Publisher: Taylor & Francis Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lsyc20

Formal Synthesis of Ambrox[®] and 9-Epiambrox

M. Cortés^a, V. Armstrong^a, M. E. Reyes^a, J. López ^a & E. Madariaga^a

^a Facultad de Química. Pontificia Universidad Católica de Chile, Casilla 306. Correo 22., Santiago, Chile Published online: 21 Aug 2006.

To cite this article: M. Cortés , V. Armstrong , M. E. Reyes , J. López & E. Madariaga (1996): Formal Synthesis of Ambrox[®] and 9-Epiambrox, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:10, 1995-2002

To link to this article: http://dx.doi.org/10.1080/00397919608003554

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <u>http://www.tandfonline.com/page/terms-and-conditions</u>

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to

date. The accuracy of any instructions, formulae, and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand, or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

FORMAL SYNTHESIS OF AMBROX® AND 9-EPIAMBROX

M. Cortés*, V. Armstrong, M. E. Reyes, J. López and E. Madariaga

Facultad de Química. Pontificia Universidad Católica de Chile. Casilla 306. Correo 22. Santiago, Chile.

Abstract. (-)-Drimenol (5) was used as starting material for the synthesis of diastereoisomeric diols 3 and 4, through the nitrile 7, Compounds 3 and 4 are the direct precursors of Ambrox (1) and 9-epiambrox (2).

Ambergris is one of the most valuable perfumes^{1,2} like civet, musk and castoreum. This substance is a metabolic product of the spermwhale (*Physeter* macrocephalus L.) that accumulates in the gut of the animal.

The most important equivalent of this scarce natural source is the norlabdane oxide Ambrox® (1) (trade name of Firmenich). For this reason diverse synthetic routes to 1 have been developed.³

On the other hand at the present time (-)-9-epiambrox (2) has been found to possess the strongest odor⁴ and the lowest treshold concentration (0.15 ppb) than that of any known analogue including Ambrox[®].



1995

Copyright © 1996 by Marcel Dekker, Inc.

To the best of our knowledge only two synthesis of 2 have been described. One of this uses sclareolide as chiral starting material⁴ and the other⁵ start with readily available precursor but involves eleven steps with an overall yield of 11%.

Following our studies on the transformation of the main component of *Drimys Winteri* to obtain compounds with ambergris-like odours^{6,7,8}, we now describe a formal synthesis of 1 and 2 which involves an alternative access to the bicyclic diols 3 and 4, the direct precursors of 1 and 2 respectively.^{9,4} The starting material was the sesquiterpene (-)-drimenol (5) readily available from the bark of *D.Winteri*.¹⁰



The hydroxyl group of 5 was mesylated with mesyl chloride in pyridine to give mesylate 6 in 90% yield. The mesyl group was replaced by a nitrile group by treatment of 6 with NaCN under phase transfer catalysis.¹¹ Nitrile 7 could be obtained in 60% yield acompanied by 27% of diene 8. Hydrolysis of nitrile 7 under Huang-Minlon conditions gave the acid 9 in 84% yield. Lactonization of compound 8 with p-toluensulfonic acid in chloroform gave (-)-8-epi-12-nor-ambreinolide (10) in 75% yield. All physical constants and spectroscopic data of 10 were consistent with those recorded in the literature.^{12,13} Reduction of lactone 10, with lithium aluminium hydride afforded diol 3 in 86% yield. According Büchi

Compound Carbón	6	7	9	10	3	12	4	
1	39.6	39.6	39.2	40.8	39.3	38.2	38.0	
2	18.6	18.6	18.8	18.3	18.3	18.1	18.5	
3	41.9	41.8	42.0	41.7	42.2	41.9	42.2	
4	32.9	32.9	32.9	32.9	33.3	32.8	32.8	
5	49. 7	49. 7	49.7	51-5	54-7	46-5	46.4	
6	23.5	23.4	23.7	18,0	18.1	19.2	20.8	
7	124.6	124.9	122.3	35.1	42.2	37.1	36.1	
8	131.1	131.1	133.4	85.7	73.0	85.9	73.0	
9	21.9	51.6	50.4	54.7	55.9	56.8	57.7	
10	36.1	36.4	36.0	36.0	38.8	35.9	38.6	
11	68.2	14.9	32.3	32.4	28, 7	32.6	29.4	
12		120.8	122.9	177.8	65.0	175.5	64.5	
17	53.7	21.6	21.8	30.0	30.3	27.3	32.0	
18	33.2	21.9	21.4	22.2	21.7	22.8	33.1	
19	21.6	33.1	33.1	33.6	33.3	33.4	21.2	
20	14.6	13.9	14.0	14.6	15.2	21.8	24.5	

Table ¹³C NMR data (CDCl₃, 50.3 MHz)

СН3-ОЅО 237.5

Numbering



and Wuest⁹ refluxing racemic **3** in nitromethane in the presence of p-toluensulfonic acid gave the kinetic cyclization product Ambrox® in excess. The ratio of the diasteroisomers **1** and **11** in the cyclization of **3** proved to be only temperature dependent. Decreasing the temperature from 80°C to 20°C afforded the kinetic diasteromer **1** almost exclusively.¹⁴

On the other hand we attempted the one-pot hydrolysis-lactonization of nitrile 7 through acid catalyzed reaction. Treatment of 7 with aqueous 2N HCl under reflux conditions for 8 hours gave 9-epi-12-norambreinolide (12) in 70% yield. It is assumed that reaction proceed through a well known isomerization of lactone $10.^4$ The physical properties and spectroscopic data of 12 were almost identical with the data kindly sent to us by Dr. Ohloff. Finally compound 12 was reduced with lithium aluminium hydride to gave diol 4 in 82% yield.

In conclusion we have develoved a simple and inexpensive methodoly for the preparation of chiral diols 3 and 4 from a readily available starting material.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Optical rotations were obtained for solutions in Chloroform (g/100 ml) on a Perkin Elmer 241 polarimeter. Unless otherwise specified I.R. spectra were recorded from KBr disc with a Perkin Elmer 1310 spectrophotometer. ¹H-NMR and ¹³C NMR spectra were recorder on a Bruker AM 200 spectrometer. Chemical shifts are reported in ppm downfield relative to tetramethylsilane (δ scale) in CDCl₃ solutions. Carbon substitution degree were established by DEPT pulse sequence. High resolution mass spectrometry were performed on a Bruker CMS 47 FT-ICR spectrometer using an ionizing voltage of 70 eV. For analytical TLC Merck silica gel 60G in 0.25 mm thick layers was used. Chromatographic separations were carried out by convential column on Merck silica gel 60 (70-230 mesh) using hexane-AcOEt mixtures of increasing polarity.

11-Mesyloxi-7-drimene (6)

To 3.61 g (16.26 mmol) of (-)drimenol (5) in 40 ml of dry pyridine was added 2.77 g of mesylchloride (24.3 mmol). The mixture was stirred at room

temperature for 40 h, then poured into water (30 ml) and extracted with AcOEt (3x50 ml). The combined organic layers were washed with HCl (5%), saturated NaHCO₃ solution, water, dried (Na₂SO₄) and concentrated in vacuo Chromatography of the residue gave 4.38g (90%) of **6** as a colourless oil. $[\alpha]_D^{20}$ = +11.3(c, 1.46). IR (neat). 2880, 1460, 1360, 1180, 960 cm⁻¹; ¹H NMR: 0.81(3H, s, CH₃), 0.85(3H, s, CH₃), 0.87(3H, s, CH₃), 1.71(s, 3H, CH₃-C₈), 3.0(3H, s, CH₃-SO₃-), 4.25(dd, J 10, 6Hz, 1H, H₁₁), 4.37(dd, J 10,3Hz, 1H, H₁₁); 5.5(broad s, 1H,H₇). H RMS calc for C₁₅H₂₄O (M⁺-CH₃SO₂H), 220.1827, found, 220.1826; calc. for C₁₅H₂₄ (M⁺-CH₃SO₃H), 204.1878, found, 204.1877.

13,14,15,16-tetranor-7-labden-12-nitrile (7)

Mesylate **6** (4.38 g, 14.6 mmol) was dissolved in toluene (60 ml) and allowed to react at 100°C with a solution of KCN (4.75g, 73 mmol) in water (37 mol) in the presence of Adogen 464 (1.67 g). After 5 h the reaction mixture was cooled, the organic layer was separated and the aqueous layer was extracted with AcOEt (3x50 ml). The combined organic phases were washed with water, dried (Na₂SO₄) and evaporated in vacuo to furnish 5.01 g of crude product. Column chromatography on silica gel gave 0.82 g (27.5%) of diene **8** and 2.02 g (60%) of the nitrile 7, as a colourless oil. $[\alpha]_D^{20^\circ} = -7.95(c,0.5)$. I.R. (neat) 2880, 2840. 2240 (CN), 1430 cm⁻¹; ¹H NMR: 0.85(s, 3H, CH₃), 0.87(s, 3H, CH₃), 0.89(s, 3H, CH₃), 1.8(broad, s, 3H, CH₃-C₈), 2.1-2.5(m, 2H, H₁₁), 5.6 (broad s, 1H, H₇). HRMS. Calc. for C_{16H25}N, 2.31. 1986. found, 231.1985.

13,14,15,16-tetranor-7-labden-12-carboxilic acid (9)

A mixture of the nitrile 7 (0.235 g, 1.02 mmol), potassium hydroxide (0.150 g, 2.7 mmol) and ethylen glicol (25 ml) was refluxed for 24 h. The mixture was cooled, diluted with water (20 ml), and then treated with 10N HCl (pH₃). The solution was extracted with AcOEt and the organic phase was washed with water, dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by column chromatography to give the acid 9 (0.22 g, 84.6%) m.p. 118-120°C (hexane), $[\alpha]_D^{20^\circ} = -6.3(c,0.94)$. I.R. 1710, 1280 cm⁻¹. ¹H NMR: 0.75(s, 3H, CH₃), 0.87(s, 3H, CH₃), 0.88(s, 3H, CH₃), 1.60(s, 3H, CH₃-C₈), 2.3-2.5(m, 2H, H₁₁), 5.43(broads, 1H, H7). H RMS Calc. for C₁₆H₂₆O₂m 250. 1932 found 250. 1933.

(-)-8β,12-epoxy-13,14,15,16-tetranorlabdane-12-one (10)(12)-nor-8-epi-ambreinolide; isosclareolide)

A mixture of 9 (1.56 g, 6.6 mmol) and p-toluensulfonic acid monohydrate (0.4 g, 21 mmol) in chloroform (30 ml) was refluxed for 1 h. The mixture was cooled, washed with NaOH (15%), water and dried (Na₂SO₄). The solvent was destilled under reduced pressure to give an oil which solidified on standing. Recristallization from hexane afforded lactone 10 (1,24 g, 75%) m.p. 89-90°C (lit¹² m.p. 92-93°C); $[\alpha]_D^{20^\circ} = -31.6^\circ$ (C, 0.4) (lit¹² $[\alpha]_D^{20^\circ} = -32.7^\circ$). IR 1770, 1140 cm⁻¹ ¹H NMR; 0.87(s, 3H, CH₃), 0.91(s, 6H, 2xCH₃), 1.32(s, 3H, CH₃), 1.75(d, 1H, J 7Hz, H-C₉), 2.35(d, 1H, J 18Hz, H-C₁₁), 2.73(dd, 1H, J 7,18 Hz, H-C₁₁). H RMS Calc. for C₁₆H₂₆O₂ 250.1932, found 250-1933.

(+)-13.14.15.16-tetranor-86,12-labdanediol (3)

To a mixture of lithium aluminium hydride (0.61 g, 16 mmol) and dry THF (80 ml) stirred under nitrogen at room temperature, was added a solution of 10 (1.0 g, 4 mmol) in dry THF (30 ml). After stirring for 3 h at room temperature, the excess of lithium aluminium hydride was destroyed by careful addition of AcOEt and an aqueous solution of HCl (10%). The mixture was extracted with AcOEt and the organic phase was washed with NaHCO3, water, dried and concentrated. The residue was chromatographed in silica to give 0.91 g (86%) of diol **3** m.p. 188-190°C (Hexane-acetone) (lit15 187-190°C); α] $_{D}^{20^{\circ}}$ = +13°C (c,0.3).IR 2880, 1460, 1370 cm⁻¹ ¹H-RM: 0.83(s, 3H, CH₃), 0.87(s,3H, CH₃), 0.97(s, 3H, CH₃), 1.14(s, 3H, CH₃-C₈); 3.61(m, 2H, H-C₁₂). H RMS. Calc. for C₁₆H₃₀O₂, 254.2245, found, 254.2244.

(-)-8 α ,12-epoxy-9-epi-13,14,15,16-tetranorlabdane-12-one (12) (12-nor-9-epiambreinolide,9-epi-sclareolide)

A mixture of nitrile 7 (1.86 g, 8.05 mmol) and HCl 6N (300 ml) was heated at reflux temperature for 8 h. After cooling the mixture was extracted with AcOEt and the organic phase was washed with water, dried and concentrated. The residuo was purified by chromatography which gave 1.04 g (70%) of lactone 12. m.p. 132-134°C (hexane-acetone), ¹⁶ $[\alpha]_{D}^{23} = -48.61(c, 0.3).^{16}$ I.R 2870, 1770, 1230, 1080 cm⁻¹, ¹H RMN: 0.82(s, 3H, CH₃), 0.91(s, 3H, CH₃), 1,1 (s, 3H, CH₃), 1,54(s, 3H, CH₃-C₈), 2.44(dd, J 8,17 Hz, 1H, H-C₁₁), 2.51(dd, J 14, 17 Hz, 1H, H-C₁₁). HRMS Calc. for $C_{16}H_{26}O_2$, 250, 1932, found 250. 1933.

(9βH)-13,14,15,16-tetranor-8α,12-diol (4)

To a stirred mixture of lithium aluminium hydride (0.6 g, 16 mmol) in dry THF (70 ml) was added a solution of lactone 12 (1.0 g, 4 mmol) in dry THF (25 ml) and the mixture was stirring at room temperature for 5 h.

After working-up as it was described for **3**, **4** (0.87 g, 82,2%) was obtained m.p. 108-110° (hexane-acetone)(lit¹⁷ 110-111°C $[\alpha]_D^{20} = -15°(c, 0.8)(lit^{17}-13-6°)$ I.R. 3380, 2880, 1460. 1380 cm⁻¹. ¹H NMR: 0.78(s, 3H, CH₃), 0.85(s, 3H, CH₃), 1.09(s, 3H, CH₃), 1.49(s, 3H, CH₃-C₁₇), 3.39(1H, ddd, J 9.3, 3.63, 5.5, H-C₁₂); 3.75(1H, ddd, J 9.3, 4.5, 10.2, H-C₁₂°). H RMS. Calc. for C₁₆H₃₀O₂, 245. 2245, found 254. 2246.

ACKNOWLEDGEMENTS

We thank "Fondo Nacional de Ciencia y Tecnología" (FONDECYT Grant N° 1930453) for financial support. Authors wish to acknowledge Dr. G. Ohloff, Firmenich S.A. Research Laboratories, Geneva, Switzerland for supplying spectral data of **3**, **10** and **12** for identification and Dr. Gerard Aranda, Ecole polytechnique CNRS, Cedex, France for High resolution mass spectra.

REFERENCES AND NOTES

- Ohloff, G. The Frangance of Ambergris. In Fragance Chemistry. The science of the sense and smell. Edited by E.T. Thiemer Academic Press, New York, 1982, pp. 535-573.
- 2. Sell, C. Chemistry and Industry, 1990, 20, 516.
- 3. Barton, D.H.R., Taylor, D.K. and Tse, C. Tetrahedron Lett. 1994, 35, 9505 and references cited therein.

- 4. Ohloff, G., Giersch, W., Pickenhagen, W., Furrer, A. and Frei, B., Helv. Chim. Acta 1985, 68, 2022.
- 5. Makeczka, R.E. Jr. and Paquette, L.A. J. Org. Chem. 1991, 56, 6538
- 6. Cortés M., and López J. Nat. Prod. Lett. 1994, 5, 183.
- 7. Peña, W., López, J. and Cortés, M. Bull. Soc. Chim. Fr. 1992, 129, 168.
- López, J. Trespalacios, C., Peña, W. and Cortés, M. Synth. Commun. 1992, 22, 2599.
- 9. Büchi, G. and Wuest, H. Helv. Chim. Acta, 1989, 72, 996.
- 10. Appel, H.H., Brooks, C. J.V. and Overton, K.H.J. J. Chem. Soc. 1959, 3322.
- 11. Heissler, D. and Ladenburger C. Tetrahedron, 1988, 44, 2513.
- Ohloff, G., Vial, C. Demole, E. Enggist P., Giersch, W., Yegou, E. Caruso, A. J. Polonsky J and Ledered, E. Helv. Chim. Acta, 1986, 69, 163.
- 13. Cambie, R.C., Joblin, K.N. and Preston, A.F. Aust. J. Chem. 1971, 24, 583.
- 14. Barrero, A.F., Altarejos, J., Alvarez-Manzaneda E.J., Ramos, J. M. and Salido, S. Tetrahedron, 1993, 49, 6251.
- 15. Hinder, M. and Stoll, M. Helv. Chim. Acta, 1954, 37, 1866.
- 16. The physical constants of 12 kindly informed to us by Dr. Ohloff were m.p. 133-135°C; $[\alpha]_{D}^{20} = -50.8^{\circ}$
- 17. Ohloff, G. and Giersch, W. Croat. Chem. Acta. 1985, 58, 491.

(Received in the USA 11/16/95)