

MEDICINAL PLANT COMMUNICATIONS

Med. plant commun

3 (1): 5 - 11 (2020)

© / ISSN 2452 4433

Short Communication

FROM THE NATURAL TO THE SYNTHETIC, A JOURNEY THROUGH
THE DESERT OF TARAPACA, CHILE

[DE LO NATURAL A LO SINTETICO, UN VIAJE POR EL DESIERTO DE TARAPACA, CHILE]

Julio Benites^{1,2} & Jaime A. Valderrama¹¹Química y Farmacia. Facultad de Ciencias de la Salud, Universidad Arturo Prat, Iquique, Chile²Facultad de Farmacia y Bioquímica, Universidad Nacional de Trujillo, Trujillo, Perújuliob@unap.cl

Abstract: The preparation of oxygenated derivatives of ambrox and isoambrox is described. The compounds have been synthesized from (-)-drimenol, (-)-polygodial and (+)-confertifolin readily available from the bark of *Drimys winteri*. The synthesis of valuable precursor of biological active compound named 5-hydroxy-1,4-naphthoquinone (**16**, juglone) via solar photo-induced reactions from 1,5-dihydroxynaphthalene **15** in green solvent media is reported. The sensitized photooxygenation of **15** “on water” and “in water” containing sodium dodecyl sulfate produce juglone **16** in 81 and 39% yields respectively.

Keywords: Ambrox; Isoambrox; Ambergris; Solar light; Photooxygenation; Green chemistry

Resumen: Se describe la preparación de derivados oxigenados de ambrox e isoambrox. Los compuestos han sido sintetizados a partir de (-) drimenol, (-) - poligodial y (+) - confertifolina fácilmente disponibles en la corteza de *Drimys winteri*. Se informa la síntesis de un precursor valioso que es biológicamente activo denominado 5-hidroxi-1,4-naftoquinona (**16**, juglona) mediante reacciones solares fotoinducida a partir de 1,5-dihidroxinaftaleno **15** usando solventes verdes. La fotooxigenación sensibilizada del compuesto **15** “en agua” y “en agua” que contiene dodecil sulfato de sodio produce juglona **16** con rendimientos de 81 y 39% respectivamente.

Palabras clave: Ambrox Isoambrox; Ámbar gris; Luz solar; Fotooxigenación; Química verde.

Received: 13 de Septiembre de 2019

Accepted: 16 de Septiembre de 2019

Published online: 30 de Septiembre de 2019

This article must be cited as: Benites J, Valderrama JA. 2019. From the natural to the synthetic, a journey through the desert of Tarapaca, Chile. *Med Plant Commun* 2 (4): 5 – 11.

Inaugural Conference VII Latinamerican Congress of Medicinal Plants, Cuenca, Ecuador, Septiembre 4-6, 2019.

INTRODUCCIÓN

Ambergris is one of the most valuable animal perfumes, like civet, musk and castoreum [1,2]. This substance is a metabolic product of the blue whale (*Physeter macrocephalus*) sperm that accumulates in the gut of the animal. It has been used for centuries because of its unique fragrance and fixative properties [3], but is now commercially banned or taken off the market thanks to the Marine Mammals Protection Act. Extensive reviews with detailed studies correlating their structure with smell, synthetic efforts, etc., are available [4]. The most important equivalent of this scarce natural source is the norlabdane oxide Ambrox® (1) (trade name of Firmenich SA). The growing demand for ambergris-type odorants has stimulated an intense search for substitutes. For this reason, various synthetic routes to Ambrox 1 and Isoambrox 2 have been developed [5-10].

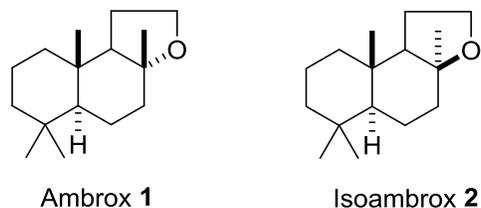


Figure No. 1
Structures of Ambrox and Isoambrox

Using the framework of our studies of natural sesquiterpenes to provide materials for the preparation of various ambergris type compounds [11-13], we are now describing the formal synthesis of the oxygenated derivatives of Ambrox and Isoambrox 3, 4, 5, 6, 7 and 8. The starting material was the sesquiterpene (-)-drimenol, readily available from the bark of *Drimys winteri* [14].

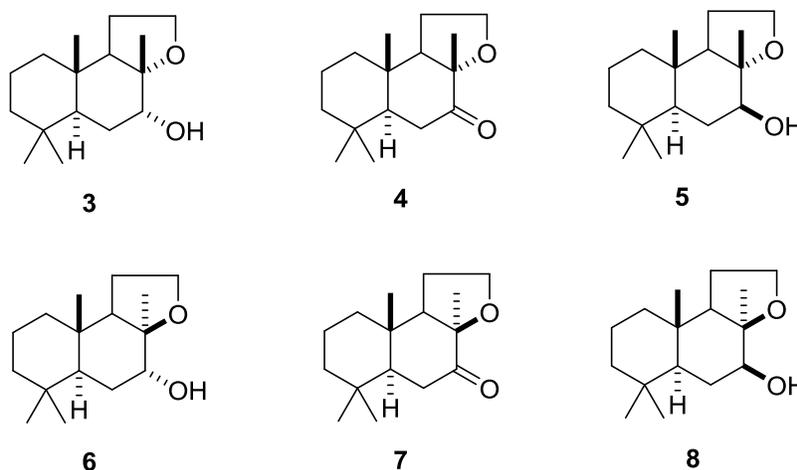


Figure No. 2
Structures of Oxygenated derivatives of Ambrox and Isoambrox 3-8

Cyclic acetals with 1,3-dioxane rings, such as Magnolan® 9 are very important odorants in the composition of perfumes [15]. Some of these acetals possess odoriferous properties related to Ambergris, in particular 10 [1], 11 [15,16] and its higher homologue 12 (Figure No. 3) [17]. In relation with our research on odorant heterocycles, we have previously reported the partial syntheses of Ambrox® [18,19] and Ambroxide [20,21].

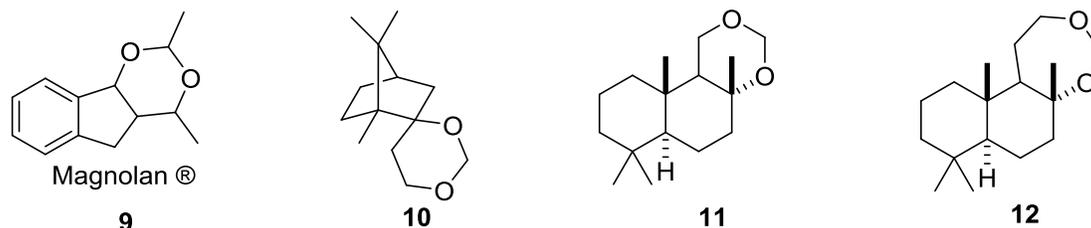


Figure No. 3
Cyclic acetals 9-12

Photochemical reactions carried out with sunlight are particularly interesting in the context of green chemistry due to substrate activation often occurs without additional reagents, which diminishes formation of by products, and the renewable nature of the energy source [22-25]. Over the last few decades, the growing demand for environmentally friendly technologies has attracted rising attention in synthetic organic photochemistry [26,27]. Solar photoacylation of 1,4-naphthoquinone **13** with furfural to give acylhydroquinone **14** and sensitized photooxygenation of 1,5-dihydroxynaphthalene (1,5-DHN) **15** that provides 5-hydroxy-1,4-naphthoquinone (**16**, juglone) are two representative examples of solar light-mediated synthesis in the field of quinoid compounds (Figure No. 4). Our continuous interest on quinone chemistry together the usefulness of acylhydroquinone **14** and juglone **16** as precursors of biological active compounds led us to study greener access to these compounds.

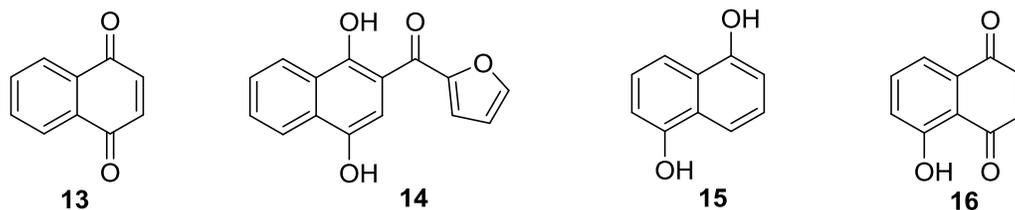


Figure No. 4
Structure of precursors 13-15 and photoproducts 14-16

RESULTS AND DISCUSSION

Preparation of oxygenated derivatives of ambrox and isoambrox from drimenol

Following our studies on the transformation of the main component of *Drimys winteri* to obtain compounds with ambergris-like odours, [12,14,19] we now describe a formal synthesis of the oxygenated derivatives of Ambrox and Isoambrox, **3**, **4**, **5**, **6**, **7** and **8**, which involves an alternative access to **17**, the direct precursor of **3**, **4**, **5**, **6**, **7** and **8**. The starting material was the sesquiterpene (-)-drimenol readily available from the bark of *D. winteri*. Epoxidation of 8-methyl-12-acetoxy-7,8-drimene **17** with mCPBA in CH_2Cl_2 at 0°C gave the α -epoxide **18** (69% yield). The compound was characterized by ^1H NMR and ^{13}C NMR spectra. The α -stereochemistry for the C-7 proton is indicated by the W1/2 value (7 Hz) of the signal at δ 2.96. These results led us to the conclusion that the reagent attacks from the less hindered α -face of the double bond, and the stereochemistry of the epoxide was consequently assigned as α . Surprisingly, treatment of **17** with LiAlH_4 led us to the 7 α -hydroxyisoambrox **6** in 23% yield and produced a mixture of epimeric diols. Compound **6** was characterized by ^1H NMR spectroscopy, which showed multiplet at δ 3.66-4.11, which was assigned to H-7 + H-12. The INEPT ^{13}C NMR spectrum showed the signal of C-12 at δ 65.7 (CH₂), the signal of C-7 at δ 70.4 (CH), and the signal of C-8 at δ 85.4 (C), confirming that it was joined to the oxygen. The stereochemistry of **6** has been established by comparing the spectrum of ambrox and isoambrox using Beierbeck and Saunders parameters [28]. All other signals were in agreement with those found for drimane models [12,19]. Besides, chemical support for the structure of compound **6** was obtained by $(\text{t-BuO})_3\text{AlH}$ reduction of **19**. Spectroscopic data were in agreement with the values reported for LiAlH_4 reduction. Oxidation of **17** with OsO_4 and co-oxidant N-methylmorpholine N-Oxide in acetone, t-butyl alcohol and water gave the mixture of acetyl diols in 98% yield.

Attempts to separating this mixture did not give acceptable results and it was decided to try saponification. After separation, the triols **20** and **21** were identified by ¹H NMR. Triols **22** and **23** were used as the starting materials for the synthesis of derivatives of ambrox and isoambrox. The cyclization of **22** and **23** to give 7 α -hydroxyambrox **3** and 7 β -hydroxyisoambrox **8** was carried out in 95% and 36% yields, respectively, using mesyl chloride in pyridine. The stereochemistry of the C-7 hydroxyl group in compound **8** is confirmed by the W1/2 value (24 Hz) of the signal at δ 3.31. Oxidation of 7 α -hydroxyambrox **3** and 7 β -hydroxyisoambrox **8** with PCC reagent in CH₂Cl₂ gave the corresponding ketones **4** and **7** in 99% and 95% yields. These ketones were characterized by ¹³C NMR spectrum showed the chemical shifts of C-7 at δ 208.7 and 213.2 respectively, clearly deshielded when compared with C-7 of **3** and **8**. Chemical support for the stereochemistry of compound **3** was obtained by Huang-Milong reduction of **4**, which gave ambrox in 90% yield. Its spectroscopic data were in agreement with the values reported by Cortés [13]. Finally, reduction of 7-oxoambrox **4** and 7-oxoisoambrox **7** with (t-BuO)₃AlH gave 7 β -hydroxyambrox **5** and 7 α -hydroxyisoambrox **6** in 50% and 61% yield, respectively.

Cyclic acetals related to Ambergris and their olfactory evaluation

We report the preparation and olfactory evaluation of eight chiral cyclic acetals (**30-37**), structurally related to **11** and **12**. The diol and triol precursors of the cyclic acetals, were prepared previously from natural (-)-polygodial and (+)-confertifolin [29-31] (Figure No. 5).

Acetals were prepared by treatment of the corresponding alcohols with para-formaldehyde and p-toluenesulfonic acid in anhydrous THF at room temperature. Acetalisation of triol **24** gave two products: **30** (32%) and **31** (50%). Oxidation of the latter with PCC, gave the corresponding aldehyde. The ¹H NMR of the oxidised product showed a doublet at 9.92 ppm (J = 2.1 Hz). When acetal **34** was treated with PCC only the starting material was recovered. Oxidation of **36** gave aldehyde **37**, the ¹H NMR for **37** shows a singlet at 9.36 ppm. The new compounds (**30-37**) were evaluated by qualified perfumers (Givaudan, Schweiz AG). The results are summarized in Table No. 1.

Table No. 1
Olfactory evaluation of acetals 30-37

Acetal	Description
30	Extremely weak, but also slightly woody
31	Odourless
32	Almost odourless, a slight woody note
33	Weak, but a slightly woody note is present
34	Shows a green, fruity and acidic smell
35	Smell woody, a bit ambery
36	Weak, woody
37	Acidic, woody odour

With the exception of **34** and the odourless **31**, all compounds exhibited a weak woody note. Odourless **31** differs from the rest of the cyclic acetals because the 1,3 dioxane ring is fused to C-7 and C-8. In the other heterocycles the dioxane ring is fused to C-8 and C-9, and these exhibit some odour. Only compound **35** possessed an ambery odour. It is structurally similar to **11** and **12**. The rest of the cyclic acetals which were prepared, contained either double bonds or hydroxyl groups, making an important difference with the structure of **11** or **12**. Comparison of **35** with the previously described seven member acetal **12**, suggests that the stereochemistry and the methylene acetal position could be of importance in the note intensity. The absence of a methyl group at C-8 as in **12**, and the presence in **35** of a methylene instead, could also be an important structural feature. In conclusion this work is a contribution to structure odoriferous properties relationship in this series.

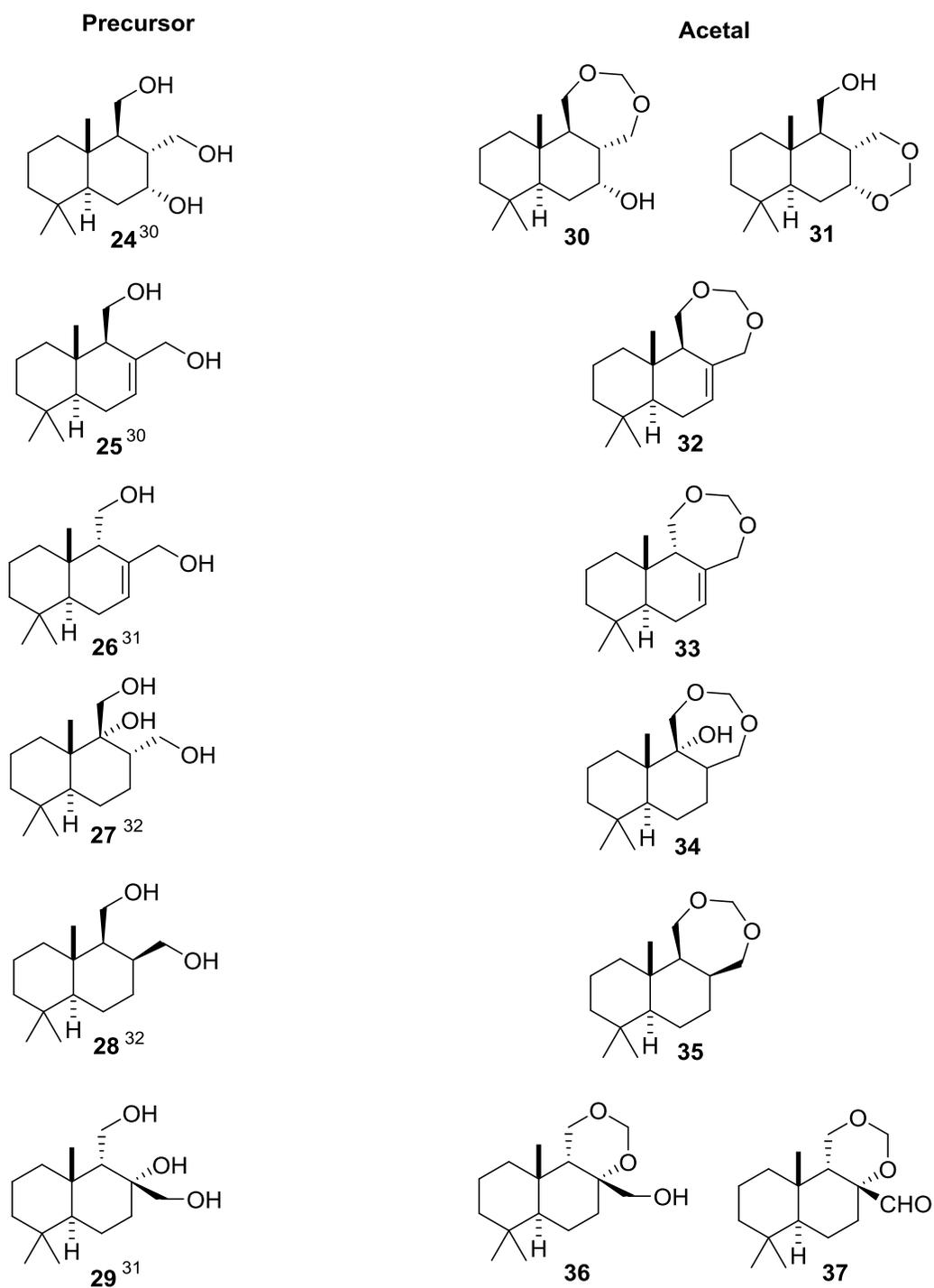


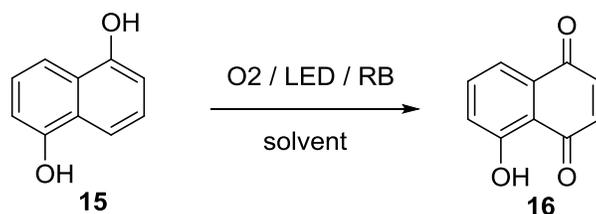
Figure No. 5

Compounds 24, 25, 26 and 29 from (-)-polygodial; 27 and 28 from (+)-confertifolin

Photooxygenation of 1,5-dihydroxynaphthalene **15** in green solvent media

Then we focused on developing clean preparation of juglone **16** by sensitized photooxygenation of 1,5-dihydroxynaphthalene **15**. There are several reports on the synthesis of juglone **16** by sensitized photooxygenation of **15** in a variety of solvents including green aqueous and ionic liquid solvents [32-34]. We first carried out in door experiments on the preparation of juglone **16** from **15** in the “preferred” solvent media: water, EtOAc, i-PrOAc, EtOH, MeOH, t-ButOH, 1-ButOH, 1-PrOH, 2-PrOH, DMK and MEK. The photooxygenation assays, performed using rose bengal (RB) as sensitizer and LED lamps as radiation source, are summarized in Table No. 2.

Table No. 2
Photooxygenation of 1,5-DHN in different solvent media under LED radiation



Solvent (s)	Conversion (%)	Yield (%) ^a	Solvent (s)	Conversion (%)	Yield (%) ^a
Water	43	55	1-ButOH	43	30
EtOAc	77	17	1-PrOH	49	75
iPrOAc	55	16	2-PrOH	43	83
EtOH	62	64	DMK	46	50
MeOH	27	83	MEK	50	64
t-BuOH	44	35			

a) Determined on the initial and recovered amounts of precursor **15**

The data of these assays indicate that the photooxygenation of **15** in water; EtOH and MEK solvent media yield product **16** in moderate yields (50-64%). Better yields formation of **16** (75-83%) was achieved in MeOH; 1-PrOH and 2-PrOH solvent media. Based on the conversion of **15** versus yield formation of **16**, the photooxygenation in EtOH is the optimal experimental condition to prepare juglone **16** by LED lamps.

Based on the in door photooxygenation experiment of compound **15** “on water” and considering that water is a desirable solvent for chemical reactions for reasons of cost, safety, and environmental concerns, the out door sensitized photooxygenation of compound **15** on water was examined. The reaction was carried out under standard condition to give juglone **16** in good yield (81%) but low precursor conversion was observed (27%). Interestingly, when the photooxygenation of compound **15** was performed on water, in the presence of 5% mol of sodium dodecyl sulfate to facilitate the transfer of the lipophilic product **16** out of the aqueous medium, high precursor conversion was observed albeit the product **16** was isolated in moderate yield (39%).

CONCLUSION

In conclusion this work is a contribution to structure odoriferous properties relationship in this series **3-8** and **30-37**. Respect to photooxygenation, we have developed greener access to juglone **16** through photooxygenation procedures induced by solar light.

ACKNOWLEDGEMENTS

The authors thank Pilar Díaz, for their excellent technical assistance.

REFERENCES

[1] G Ohloff 1982. The fragrance of Ambergris. In: Fragrance Chemistry. The science of the sense and smell. ET Theimer (ed.) Academic Press, New York, USA. <https://doi.org/10.1016/B978-0-12-685850-1.50020-6>

- [2] C Sell. 1990. Chem Ind 20: 516.
- [3] S Escher et al., 1990. Helv Chim Acta 73: 1935. <https://doi.org/10.1002/hlca.19900730717>
- [4] G Frater et al., 1981. In: perfumes, art, science and technology. PM Muller, D Lamparsky (eds). Elsevier Applied Science, New York, USA.
- [5] DHR Barton et al., 1994. Tetrahedron 35: 9505. [https://doi.org/10.1016/0040-4039\(94\)88497-8](https://doi.org/10.1016/0040-4039(94)88497-8)
- [6] H Koyama et al., 1987. Tetrahedron Letter 28: 2863. [https://doi.org/10.1016/S0040-4039\(00\)96229-4](https://doi.org/10.1016/S0040-4039(00)96229-4)
- [7] R Decorzant et al., 1987. Tetrahedron 43: 1871.
- [8] IC Coste-Maniere et al., 1988. Tetrahedron Letter 29: 1017. [https://doi.org/10.1016/0040-4039\(88\)85323-1](https://doi.org/10.1016/0040-4039(88)85323-1)
- [9] PA Christenson. 1988. Tetrahedron 44: 1925. [https://doi.org/10.1016/S0040-4020\(01\)90335-7](https://doi.org/10.1016/S0040-4020(01)90335-7)
- [10] K Mori et al., 1990. Liebigs Annal Chem 361.
- [11] M González-Sierra et al., 1987. Heterocycles 26: 2801. <https://doi.org/10.3987/R-1987-11-2801>
- [12] H Maturana et al., 1984. Synth Commun 14: 661. <https://doi.org/10.1080/00397918408063752>
- [13] M Cortés et al., 1996. Synth Commun 26: 1995. <https://doi.org/10.1080/00397919608003554>
- [14] H Apple et al., 1959. J Chem Soc 3322.
- [15] P Kraft et al., 2000. Angew Chem Int Ed 39: 2980. [https://doi.org/10.1002/1521-3773\(20000901\)39:17<2980::AID-ANIE2980>3.0.CO;2-%23](https://doi.org/10.1002/1521-3773(20000901)39:17<2980::AID-ANIE2980>3.0.CO;2-%23)
- [16] RC Cambie et al., 1981. Aust J Chem 34: 1265. <https://doi.org/10.1071/CH9811265>
- [17] RC Cambie et al., 1971. Aust J Chem 24: 2365. <https://doi.org/10.1071/CH9712365>
- [18] M González-Sierra et al., 1987. Heterocycles 26: 2801.
- [19] M Cortés et al., 1996. Synth Commun 25: 1995. <https://doi.org/10.1080/00397919608003554>
- [20] H Maturana et al., 1991. Synth Commun 21: 1533. <https://doi.org/10.1080/00397919108016428>
- [21] H Maturana et al., 1984. Synth Commun 14: 661. <https://doi.org/10.1080/00397918408063752>
- [22] A Albini et al., 2004. Green Chem 6: 1. <https://doi.org/10.1039/B309592D>
- [23] J Mattay. 2002. J Chem Unserer Zeit 36: 98. [https://doi.org/10.1002/1521-3781\(200204\)36:2<98::AID-CIUZ98>3.0.CO;2-V](https://doi.org/10.1002/1521-3781(200204)36:2<98::AID-CIUZ98>3.0.CO;2-V)
- [24] A Albini et al., 2000. Pure Appl Chem 72: 1321. <https://doi.org/10.1351/pac200072071321>
- [25] AG Griesbeck et al., 1999. Green Chem 1: 205. <https://doi.org/10.1039/a905076k>
- [26] P Tundo et al., 2000. Pure Appl Chem 72: 1207.
- [27] PT Anastas et al., 1998. Green Chemistry, Theory and Practice. Oxford University Press, Oxford, UK.
- [28] M Colombo et al., 1986. Can J Chem 64: 552. .
- [29] W Peña et al., 1989. Synth. Commun 19: 2841. <https://doi.org/10.1080/00397918908052672>
- [30] M Cortés et al., 1998. J Chem Res Suplem 36.
- [31] J Benites et al., 2001. Synth Commun 31: 1347. <https://doi.org/10.1081/SCC-100104043>
- [32] O Suchard et al., 2006. Tetrahedron 62: 1467.
- [33] M Oelgemöller et al., 2011. J Phys Chem A 115: 280.
- [34] B Murphy et al., 2009. Green Chem 11: 1867. <https://doi.org/10.1039/B913252J>