Oxidative C-Ring Opening of Abietane Diterpenes with Ammonium Cerium(IV) Nitrate

Joaquín González Marrero, Lucía San Andrés,* Javier Gutiérrez Luis

Instituto Universitario de Bio-Orgánica 'Antonio González', Universidad de La Laguna, Avenida Astrofísico Francisco Sánchez 2, 38206 La Laguna, Tenerife, Canary Islands, Spain
Fax +34(922)318571; E-mail: landrest@ull.es

Received 16 November 2006

Abstract: The oxidation reaction of 11,12-di-*O*-methylcarnosol with ammonium cerium(IV) nitrate (CAN) gave an abietane diterpene with the C-ring opened and a diester function. The structure of this diester was established by spectroscopic analysis and by chemical means. The reaction of 11,12-di-*O*-dimethylgaldosol with CAN gave a similar result, yielding a δ-lactone which structure was established as 7-hydroxy-11,12-*seco*-8,13-abietadien-12,7:20,6β-dilacton-11-oic acid methyl ester by spectroscopic analysis and chemical means. These results could be useful to accede to other natural products like rosmic acid.

Key words: oxidation, abietane diterpenes, ring opening, ammonium cerium(IV) nitrate

The genus *Salvia* (Lamiaceae) consists of approximately 500 species found worldwide. *Salvia* species are used as traditional medicines all around the world for the treatment of a variety of diseases, including infectious conditions. Studies of their chemical constituents have revealed the presence of a large variety of diterpenoids with antibacterial,[1] antioxidant,[2] antidiabetic,[3] antitumor,[4] leishmanicidal,[5] and antiplasmodial[5] properties among others. Unfortunately, most of these diterpenes are almost always present in the plant in very low quantities. In previous work[6] we have reported the partial synthesis of rosmanol (**3**), rosmaquinone (**4**), 7-methoxyrosmanol (**5**), 7-ethoxyrosmanol (**6**), galdosol (**7**) and epirosmanol (**8**) from the abundant diterpene carnosol (**1**, Figure 1) as an efficient alternative method to obtain these minority compounds.

In the course of our work on the partial synthesis of these minority diterpenes and their derivatives with biological interest, we have found that ammonium cerium(IV) nitrate [$Ce(NH_4)_2(NO_3)_6$, CAN] in aqueous acetonitrile oxidizes the *o*-dimethoxyphenyl group present in the diterpene structure with the unexpected opening of the C-ring.

Castagnoli et al.[7] reported the oxidative demethylation reaction of *o*-dimethoxybenzenes with bulky substituents to the corresponding *o*-quinones and *p*-quinones (as secondary products) using ammonium cerium(IV) nitrate. When we attempted to use this reaction with abietatriene diterpenes to obtain the *o*-quinone and/or *p*-quinone derivatives, we found a completely different result with the opening of the aromatic ring and obtaining a diester derivative.

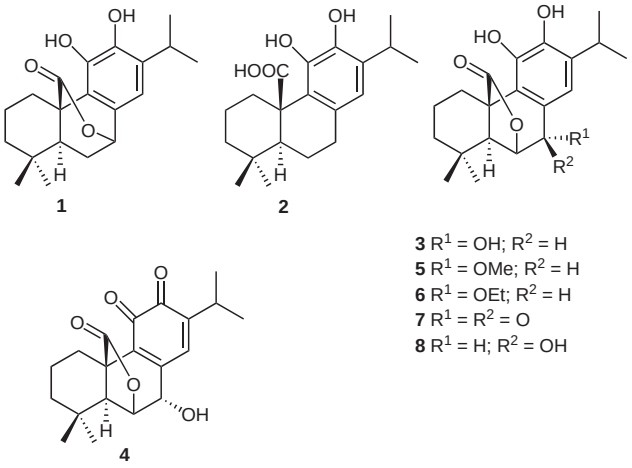
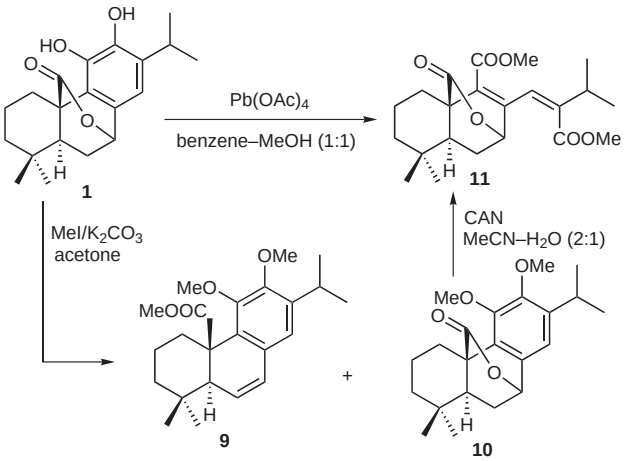


Figure 1

11,12-Di-*O*-carnosol (**10**) was obtained from carnosol (**1**), an abundant natural product of the *Salvia* species, which can also be obtained by oxidation[6] of carnosic acid (**2**), another abundant natural product, as indicated in Scheme 1. Reaction of 11,12-di-*O*-carnosol (**10**) with CAN in aqueous acetonitrile gave the diester **11** with 90% of yield (Scheme 1). The structure of **11** was established by its physical and spectroscopic data as 11,12-*seco*-8,13-abietadien-20,7β-lacton-11,12-dioic acid dimethyl ester,

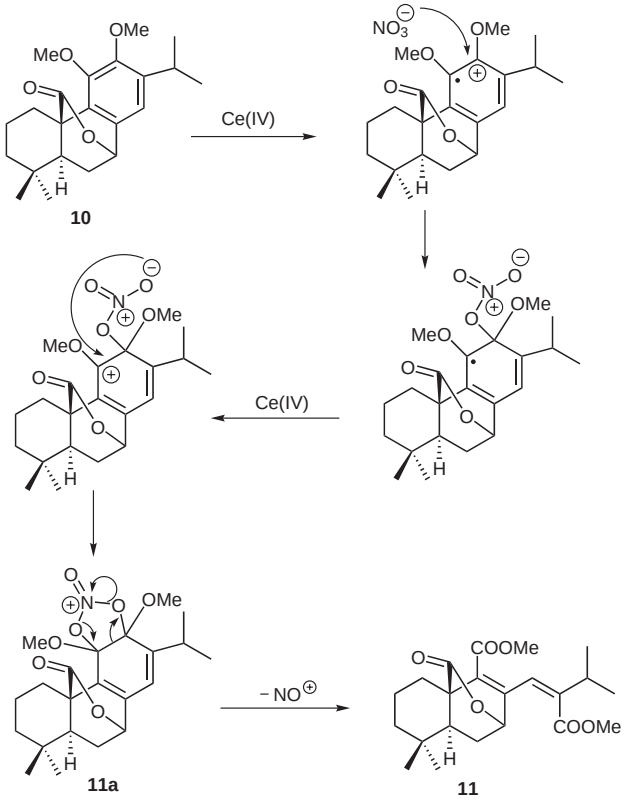


Scheme 1

SYNLETT 2007, No. 7, pp 1127–1129
Advanced online publication: 13.04.2007
DOI: 10.1055/s-2007-977418; Art ID: D34506ST

which was previously reported by us,[8] and was confirmed by chemical means. Thus, reaction of carnosol (**1**) with lead tetraacetate in benzene–MeOH yielded a product with the same structure as **11** (Scheme 1).

Recently Flowers et al.[9] described a possible and reasonable mechanism for the oxidation reactions with CAN. We can explain the formation of diester **11** applying the mechanism proposed by Flowers et al. In which after oxidation of the aromatic ring by Ce(IV) and internal ligand transfer of nitrate, leads to cyclic intermediate **11a** which by rearrangement with loss of nitroso ion gave the diester **11** (Scheme 2).

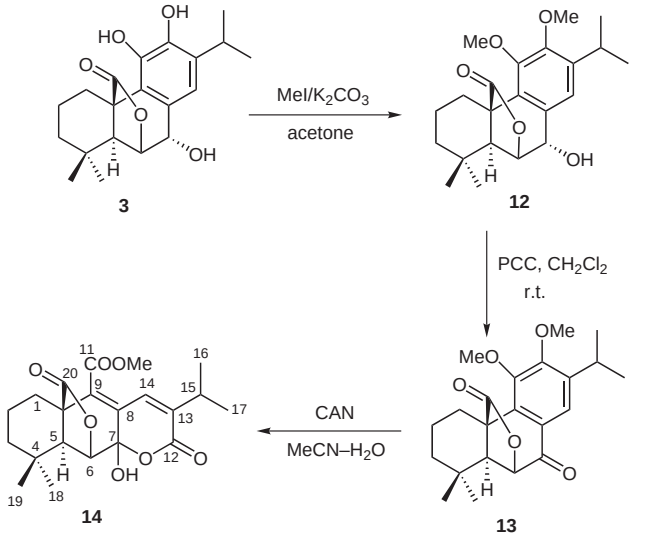


Scheme 2

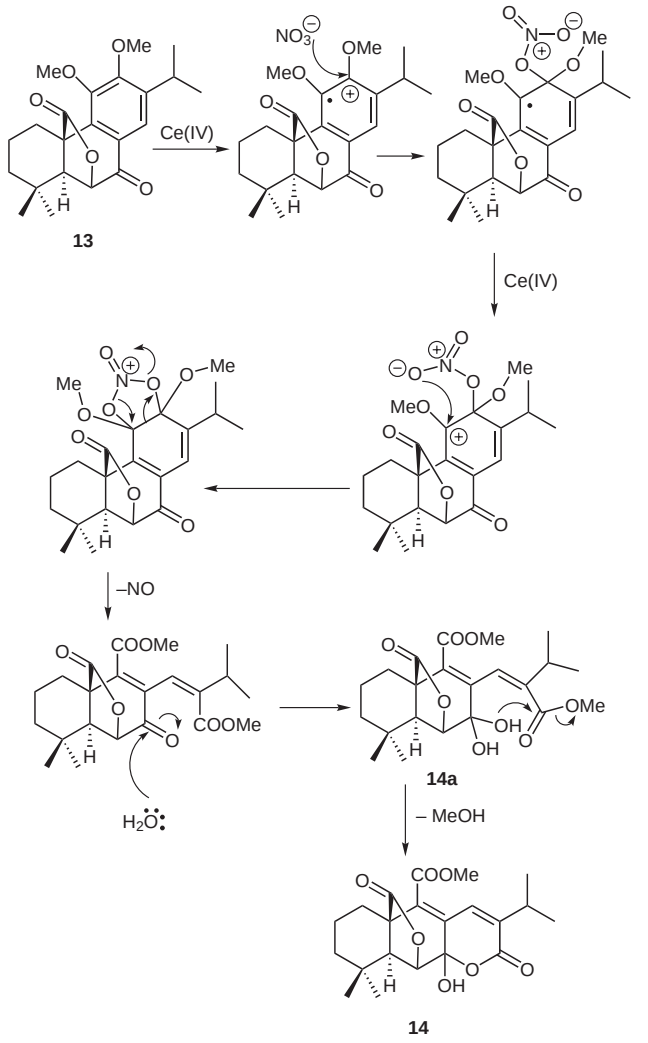
When we repeated the reaction with 11,12-di-*O*-methylgaldosol (**13**) generated from rosmanol (**3**) we obtained a compound of which physical and spectroscopic data[10] were in accordance with the lactone structure of 7-hydroxy-11,12-*seco*-8,13-abietadien-12,7:20,6β-dilacton-11-oic acid methyl ester for **14** (Scheme 3).

The formation of lactone **14** could be explained by the process shown in Scheme 4. First an oxidative C-ring opening occurs in the presence of H_2O to give the *gem*-diol **14a**, which then attacks the ester group closest to the C-7 position, resulting finally in the δ-lactone **14**.

We think that these results could be useful for accessing other natural products like rosmic acid[11] isolated from leaves of *Rosmarinus officinalis* with antimicrobial activity against *Streptomyces scabies* (the plant pathogen that causes common scab on potatoes).



Scheme 3



Scheme 4

Acknowledgment

We thank the CYTED Project IV.11 for financial support and J. G. Marrero is thankful to the CajaCanarias for a fellowship.

References and Notes

(1) Lin, L. Z.; Wang, X. M.; Huang, X. L.; Huang, Y.; Cordell, G. A. *Phytochemistry* **1989**, *28*, 3542.
(2) Dobrynin, V. N.; Kolosov, M. N.; Chernov, B. K.; Denbentseva, N. A. *Khim. Prir. Soedin.* **1976**, *5*, 686.
(3) Hitokoto, H.; Morozumi, S.; Wauke, T.; Sakai, S.; Kurata, H. *Appl. Environ. Microbiol.* **1980**, *39*, 818.
(4) Ulubelen, A.; Topcu, G.; Tan, N.; Lin, L.-J.; Cordell, G. A. *Phytochemistry* **1992**, *31*, 2419.
(5) Sairafianpour, M.; Christensen, J.; Staerk, D.; Budnik, B. A.; Kharazmi, A.; Bagherzadeh, K.; Jaroszewski, J. W. *J. Nat. Prod.* **2001**, *64*, 1398.
(6) Marrero, J. G.; San Andrés, L.; Luis, J. G. *J. Nat. Prod.* **2002**, *65*, 986.
(7) Jacob, P.; Callery, P. S.; Shulgin, A. T.; Castagnoli, N. *J. Org. Chem.* **1976**, *41*, 3627.
(8) Marrero, J. G.; San Andrés, L.; Luis, J. G. *Synlett* **2002**, 1517.
(9) Zhang, Y.; Jiao, J.; Flowers, R. A. *J. Org. Chem.* **2006**, *71*, 4516.
(10) **7-Hydroxy-11,12-*seco*-8,13-abietadien-12,7:20,6β-dilacton-11-oic Acid Methyl Ester (14)**
To a solution of 11,12-di-*O*-methylgaldosol (**13**, 19.5 mg, 0.0524 mmol) in MeCN (2 mL), was added a solution of CAN (163.2 mg, 0.298 mmol) in H_2O (1 mL). The reaction mixture was stirred at r.t. for 72 h and then H_2O (10 mL) was added, extracted with EtOAc (3 × 5 mL), washed with brine (2 × 5mL), dried over anhyd Na_2SO_4, and filtered. The solvent was eliminated under reduced pressure, and the crude product was purified by preparative TLC using *n*-hexane–EtOAc (6:4) as eluent to obtain 7-hydroxy-11,12-*seco*-8,13-abietadien-12,7:20,6β-dilacton-11-oic acid methyl ester (**14**, 9.2 mg, 44.8%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (3 H, s, Me-19), 1.04 (3 H, s, Me-18), 1.12 (3 H, d, *J* = 7.0 Hz, Me-16), 1.13 (3 H, d, *J* = 7.0 Hz, Me-17), 2.42 (1 H, br d, *J* = 9.8 Hz, H-1β), 2.61 (1 H, s, H-5), 2.92 (1 H, hept, *J* = 7.0 Hz, H-15), 3.89 (3 H, s, OCH_3), 4.79 (1 H, s, H-6), 5.15 (1 H, br s, OH), 6.91 (1 H, s, H-14). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.7 (t, C-2), 21.1 (q, C-16), 21.1 (q, C-17), 21.3 (q, C-18), 23.8 (t, C-1), 28.7 (d, C-15), 30.9 (s, C-4), 31.1 (q, C-19), 37.6 (t, C-3), 46.5 (s, C-10), 52.3 (q, OCH_3), 53.2 (d, C-5), 77.2 (d, C-6), 96.7 (s, C-7), 129.1 (d, C-14), 130.0 (s, C-8), 139.8 (s, C-9), 140.0 (s, C-13), 164.6 (s, C-12), 165.1 (s, C-11), 174.5 (s, C-20). MS (EI): *m/z* (%) = 390 (16) $[M]^+$, 345 (4), 313 (100), 303 (27), 281 (33), 272 (32), 259 (55), 231 (20), 217 (24), 197 (61), 181 (13), 166 (19), 137 (18), 69 (54). HRMS (EI): *m/z* calcd for $C_{21}H_{26}O_7$: 390.1679; found: 390.1678.
(11) Takenaka, M.; Watanabe, T.; Sugahara, K.; Harada, Y.; Yoshida, S.; Sugawara, F. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 1440.