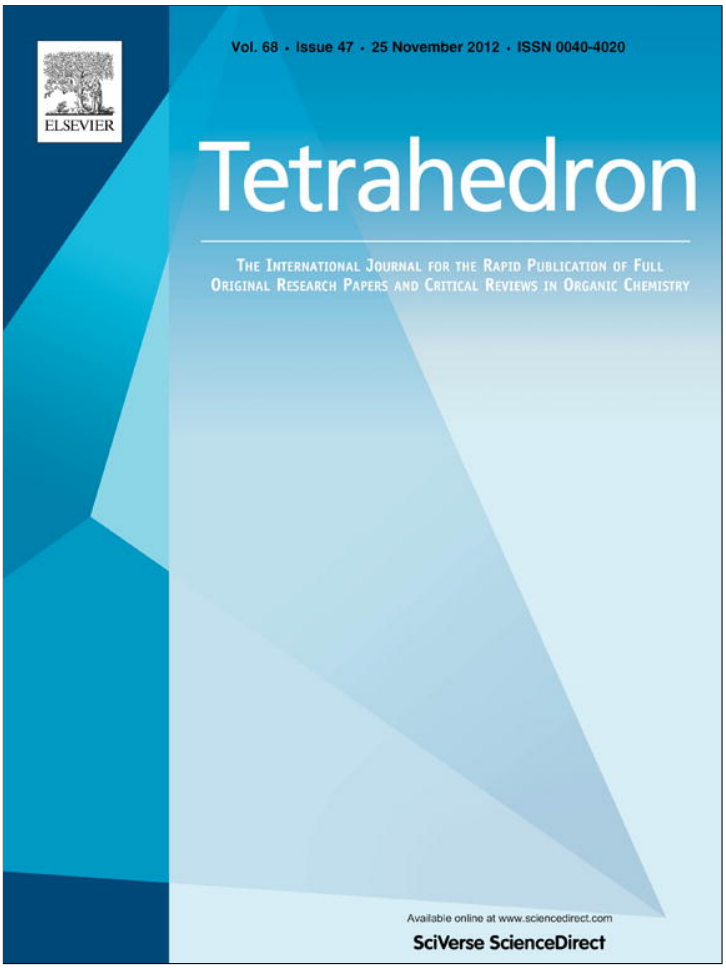


Tetrahedron 68 (2012) 9612–9615

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Short syntheses of (+)-ferruginol from (+)-dehydroabietylamine

Miguel A. González *, David Pérez-Guaita

Departamento de Química Orgánica, Universidad de Valencia, Dr. Moliner 50, 46100 Burjassot, Valencia, Spain

ARTICLE INFO

Article history:
Received 27 July 2012
Received in revised form 4 September 2012
Accepted 11 September 2012
Available online 16 September 2012

Keywords:
Diterpene
Ferruginol
Dehydroabietylamine
Deamination
Chemical synthesis

ABSTRACT

Short syntheses of bioactive (+)-ferruginol in five or six synthetic steps starting from commercially available (+)-dehydroabietylamine are described. The oxygenated function at C12 was introduced via a Friedel–Crafts acylation of *N*-phthaloyldehydroabietylamine followed by Baeyer–Villiger oxidation. Then, overall deprotection of functional groups, reductive deamination or biomimetic oxidative deamination, and final Wolff–Kishner reduction provided (+)-ferruginol in 21 and 23% overall yields, respectively.

1. Introduction

Abietane diterpenoids are widely distributed natural products in the plant kingdom with a wide range of biological activities.[1] Among them, oxidized abietane diterpenes ferruginol (**1**),[2] abietaquinone methide (**2**),[3] and nimbidiol (**3**)[4] and deoxynimbidiol (**4**)[5] (Fig. 1) have led to several synthetic and biological studies due to their interesting structure and above all their biological properties. For example, our target compound **1** occurs in plants belonging to the Podocarpaceae, Cupressaceae, Lamiaceae, and Verbenaceae families but it is of limited access and isolation protocols are time consuming. This diterpene has attracted much attention since it has exhibited promising bioactivities, such as antifungal and antimicrobial,[6] miticidal,[7] cardioactive,[8] antioxidative,[9] antiplasmodial,[10] antileishmanial and nematicidal,[11] and antiulcer properties.[12] Also, it has recently shown antitumor activity against prostate cancer by inducing apoptosis,[13] cytotoxicity against human pancreatic tumor cell lines,[14] as well as anti-inflammatory activity.[15] In addition, ferruginol (**1**) is the starting material for the synthesis of compounds **2**–**4**, which have recently exhibited potent antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE).[16]

The potent biological profile of ferruginol (**1**) has spurred the development of synthetic strategies that rest primarily on the conversion of available natural products as abietic acid,[17] dehydroabietic acid,[18] and sclareol.[19] Other strategies involve a diastereoselective polyene cyclization[20] and a tandem retro-aldol and intramolecular Friedel–Crafts alkylation sequence.[21] Nevertheless, all these strategies require lengthy multi-step syntheses and fail to deliver efficiently larger amounts of **1** for further investigation and potential applications. Herein we report a straightforward multi-gram synthetic sequence to compound **1** from commercially available (+)-dehydroabietylamine (**5**).

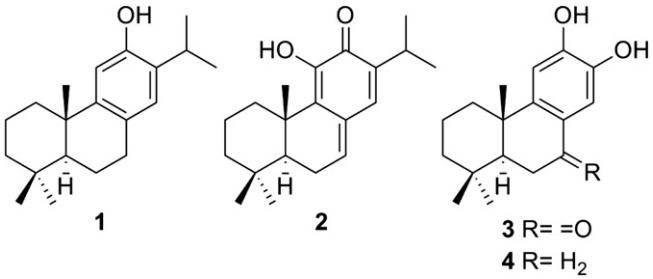


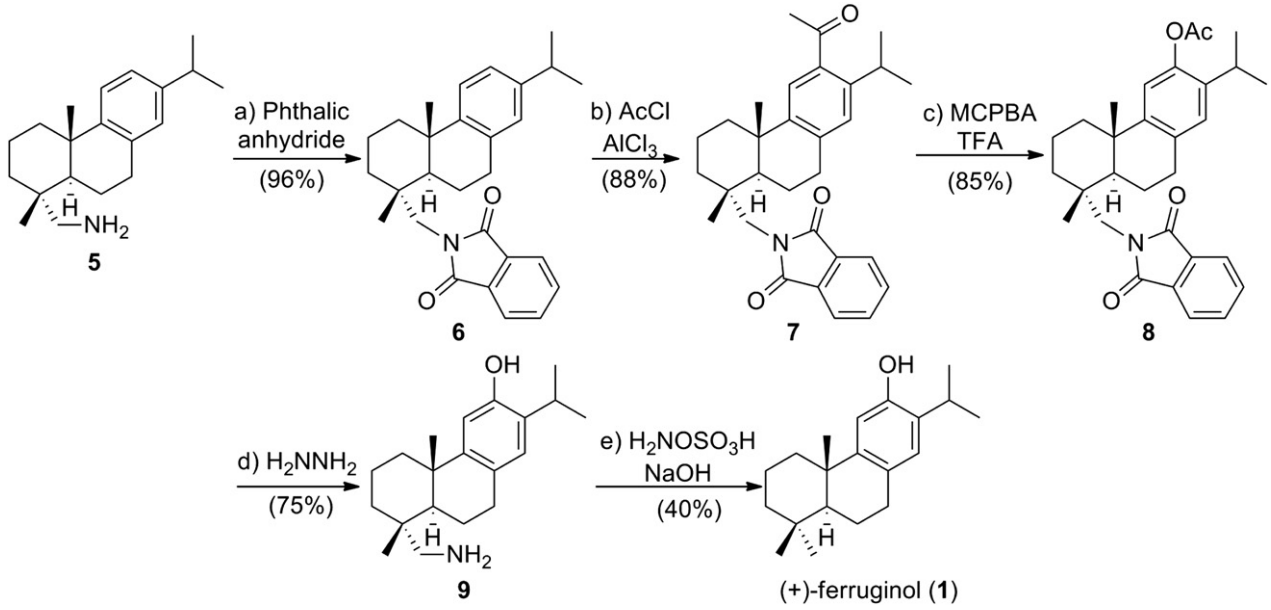
Fig. 1. Selected structures of oxidized abietane diterpenes.

2. Results and discussion

Based on the recent work of Waldvogel and co-workers,[22] the amino group in **5** is protected with the phthaloyl group to give **6** in excellent yield (96%). Then, Friedel–Crafts acylation of **6** gave acetophenone **7** (88% yield), which was oxidized under modified Baeyer–Villiger conditions, with *meta*-chloroperbenzoic acid, to afford acetate **8** in 85% yield (Scheme 1). In general, the published

* Corresponding author. Tel.: +34 96 354 3880; fax: +34 96 354 4328; e-mail address: miguel.a.gonzalez@uv.es (M.A. González).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.09.055

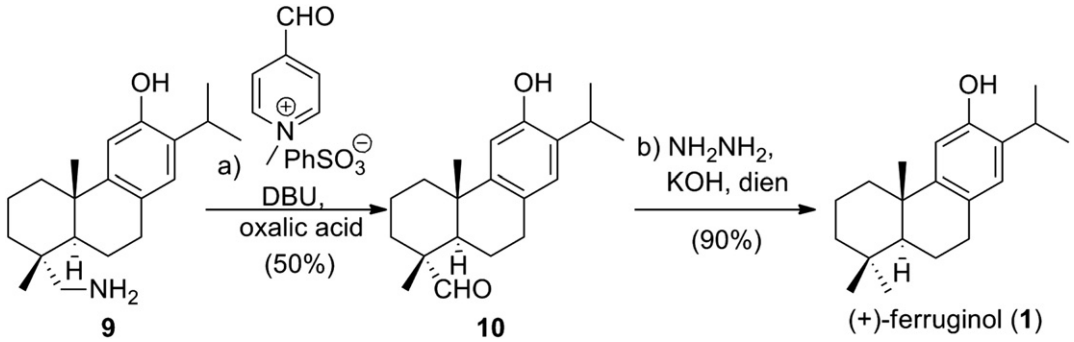


Scheme 1. Synthesis of ferruginol **1**. Method A. Reagents and conditions: (a) 4.0 equiv of phthalic anhydride, py, reflux, 96%; (b) 3.5 equiv or AcCl, 3 equiv of $AlCl_3$, DCM, 0 °C, 88%; (c) 2.6 equiv of MCPBA, 1 equiv of TFA, DCM, 0 °C, 85%; (d) 6.0 equiv of $H_2NNH_2 \cdot H_2O$, EtOH, reflux, 75%; (e) 3.0 equiv of H_2NOSO_3H, EtOH, 2.5 M NaOH, rt, 40%.

procedures worked well except the crystallizations of compounds **6** and **8** that were unsuccessful in several attempts and batches.

Then, we needed to study the deprotection of the amino and hydroxyl (as an acetate) functional groups and one step of deamination to afford the target molecule. Waldvogel and co-workers studied the selective deprotection of the phenolic alcohol but the removal of the phthalimide group was not investigated. We thought in the treatment of phthaloyl-acetate **8** under standard phthalimide deprotection conditions with hydrazine in ethanol.[23] We envisaged that, under these conditions, the cleavage of the acetate group (by hydrazinolysis) might compete with the cleavage of the phthaloyl group itself.[24] We believed that using an excess of hydrazine would probably lead to the desired amino-phenol **9**. In method of Kollonitsch and co-workers to reductively deaminate free amino groups directly by the treatment with 3–5 equiv of hydroxylamine-*O*-sulfonic acid (HOS) in aqueous basic media at rt.[26] In our case, we needed the participation of a co-solvent (ethanol) to accomplish this deamination reaction, which successfully provided the desired known ferruginol (**1**) (Scheme 1) in enantiomerically pure form but in very moderate yield (40% yield, gram scale; natural[12b] [α] +38.0 (*c* 0.5) and synthetic [α] +45.6 (*c* 2.5)). In order to improve the yield for this conversion, we tried the deamination reaction with the corresponding *p*-toluenesulfonamide by treatment with excess HOS but we did not achieve better results.

We were satisfied with the results, however, we next studied an oxidative deamination (Method B, Scheme 2), which would require



Scheme 2. Synthesis of ferruginol **1**. Method B. Reagents and conditions: (a) 1.5 equiv of 4-formyl-1-methylpyridinium benzensulfonate, 1.0 equiv of DBU, satd oxalic acid solution, DCM/DMF 3:1, rt, 50%; (b) 1.2 equiv of $H_2NNH_2 \cdot H_2O$, 3.0 equiv of KOH, diethyleneglycol, 120–220 °C, 90%.

fact, our expectations were confirmed and the new compound **9** was obtained as a result of the double deprotection in one-pot (75% yield) (Scheme 1). Finally, the last and key step to study was the deamination. It is obvious that the direct conversion into ferruginol (**1**) would require a reductive deamination (Method A, Scheme 1). This transformation has been previously achieved in moderate yield (64%, 89% based on recovered starting material) in commercial dehydroabietylamine (**5**) via an aryl sulfonamide by treatment with ethereal chloramine.[25] We wanted to avoid the increase of steps number and generation of chloramine. Thus, we choose the subsequently an additional step to obtain the target molecule by reduction of the resulting 18-oxoferruginol (**10**) (Scheme 2). To this end, after a search in the literature, we thought that the conversion of the primary amine in compound **9** into an aldehyde in multi-gram scale would be a biomimetic conversion, i.e., using Rapoport method with a 4-formyl-1-methylpyridinium salt.[27] This method mimics the biological process for transamination reactions with pyridoxal and the conditions are extremely mild and compatible with sensitive functional groups. It involves imine formation, prototropic rearrangement, and hydrolysis.

Thus, we initially treated amino-phenol **9** with 4-formyl-1-methylpyridinium iodide and DBU and hydrolysis with aqueous oxalic acid. The reaction was not clean obtaining the desired 18-oxoferruginol **10** in low yield. This problem was solved partially by utilizing 4-formyl-1-methylpyridinium benzenesulfonate eliminating the counterion oxidation–reduction interference in the transamination process. As a result, the desired aldehyde **10** was obtained in better yield and in gram scale (50%, 5-g scale).

The final reduction step has been achieved successfully in multigram scale in our lab in similar diterpenoid systems by Wolff–Kishner reduction.[28] Thus, we treated aldehyde **10** with hydrazine and KOH in diethyleneglycol in two heating steps; first at 120 °C and second at 220 °C. As a result, we obtained the desired ferruginol (**1**) (Scheme 2) in enantiomerically pure form in excellent yield (90% yield, 5-g scale).

3. Conclusion

In summary, we present herein short and convenient syntheses of the natural product (+)-ferruginol (**1**) from commercial available (+)-dehydroabietylamine (**5**). These syntheses solve the problem of availability of this diterpene for potential biomedical applications of either itself or other related derivatives, as it is an excellent starting material for the synthesis other potent bioactive molecules.

4. Experimental section

4.1. General methods

Optical rotations were determined using a 5-cm path-length cell, concentration expressed in g/100 mL, $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. NMR spectra were recorded on a 300 MHz spectrometer. All spectra were recorded in $CDCl_3$ as solvent unless otherwise described. Complete assignments of ^{13}C NMR multiplicities were made on the basis of DEPT experiments. *J* values are given in hertz. Mass spectra (MS) were run on a QTOF spectrometer. Reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60 F-254 in 0.25 mm-thick plates. Compounds on TLC plates were detected under UV light at 254 nm and visualized by immersion in a 10% sulfuric acid solution or ninhydrin and heating with a heat gun. Purifications were performed by flash chromatography on Merck silica gel (230–400 mesh). All non-aqueous reactions were carried out in an argon atmosphere in oven-dried glassware. Commercial reagent grade solvents and chemicals were used as received unless otherwise noted. Combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure.

4.2. Syntheses

*4.2.1. Synthesis of 18-aminoferruginol (**9**, 12-hydroxydehydroabietylamine).* A solution of phthalimide **8** (9.0 g, 19 mmol) dissolved in hot ethanol (175 mL) was treated with excess hydrazine monohydrate (5.5 mL, 114 mmol) and heated at reflux for 3 h. Then, without cooling a white solid was filtered off and washed with fresh ethanol. The filtrate was concentrated to give crude solid amino-phenol **9**. This solid was treated with 200 mL of 2 M NaOH and stirred for 1 h, the resulting basic solution was neutralized with approx. 200 mL of 2 M HCl, and then extracted with dichloromethane (5×80 mL). The extract was dried and concentrated to give 4.28 g (75%) of amino-phenol **9** as a pale solid, which was used without further purification: $[\alpha]_D^{20}$ +48.2 (*c* 1.7, $CHCl_3$); ^1H NMR (300 MHz) δ 6.82 (1H, s), 6.62 (1H, s), 3.15 (1H, m), 2.63 (1H, d, *J*=12.0), 2.46 (1H, d, *J*=12.0), 2.16 (1H, m), 1.23 (3H, d, *J*=6.0), 1.21 (3H, d, *J*=6.0), 1.21 (3H, s), 0.89 (3H, s); ^{13}C NMR (75 MHz) δ_C 151.3 (s), 148.1 (s), 132.1 (s), 126.5 (d), 126.3 (s), 110.9 (d), 53.6 (t), 45.0 (d), 38.5 (t), 37.3 (s), 37.0 (s), 35.2 (t), 29.4 (t), 26.7 (d), 25.2 (q), 22.6×2 (q), 18.8 (t), 18.7 (t), 18.6 (q); HRMS (ESI) *m*/*z* 302.2478 $[M+1]^+$, calcd for $C_{20}H_{32}NO$: 302.2484.

*4.2.2. Synthesis of ferruginol (**1**). Method A.* The amino-phenol **9** (5.0 g, 16.6 mmol) is dissolved in 2.5 M NaOH (32 mL) and ethanol (32 mL) and cooled to 0 °C. Then, hydroxylamine-*O*-sulfonic acid (HOS 97%, 3.6 g, 30.9 mmol) is added. After stirring for 30 min, additional 2.5 M NaOH (16 mL) and ethanol (16 mL) were added followed by 1.8 g of additional HOS and the mixture was allowed to warm to rt. After stirring at rt for 2 h, the basic solution was neutralized with concentrated H_2SO_4 dropwise, diluted with ethyl acetate (200 mL) and washed with brine, dried, and concentrated. The resulting residue (orange oil) was chromatographed on silica eluting with hexane/ethyl acetate 5:1 to give 1.9 g (40%) of the desired compound **1** as a yellowish oil: $[\alpha]_D^{20}$ +45.6 (*c* 2.5, $CHCl_3$); ^1H NMR (300 MHz) δ 6.90 (1H, s), 6.68 (1H, s), 3.20 (1H, m), 2.70–3.00 (2H), 2.16 (1H, m), 1.30 (3H, d, *J*=6.0), 1.28 (3H, d, *J*=6.0), 1.21 (3H, s), 1.00 (3H, s), 0.98 (3H, s); ^{13}C NMR (75 MHz) δ_C 150.6 (s), 148.6 (s), 131.5 (s), 127.2 (s), 126.5 (d), 111.0 (d), 50.3 (d), 41.6 (t), 38.8 (t), 37.4 (s), 33.4 (q), 33.3 (s), 29.7 (t), 26.7 (d), 24.7 (q), 22.7 (q), 22.6 (q), 21.6 (q), 19.3 (t), 19.2 (q); HRMS (ESI) *m*/*z* 287.2369 $[M+1]^+$, calcd for $C_{20}H_{31}O$: 287.2375.

*4.2.3. Synthesis of 18-oxoferruginol (**10**).* A solution of the amino-phenol **9** (5.0 g, 16.6 mmol) in DCM/DMF 3:1 (260 mL) at rt was treated with 1.5 equiv of 4-formyl-1-methylpyridinium benzensulfonate (7 g, 25 mmol) and stirred for 3 days. Next, the mixture was treated with 1 equiv of DBU (2.5 mL) and stirred for 3 h, then quenched with cold (4 °C) satd aqueous oxalic acid solution (200 mL) and stirred for 2 h. Then, the mixture was diluted with 250 mL of water and 250 mL of diethyl ether and the aqueous phase was reextracted three times with 150 mL of diethyl ether. The combined organic extracts were washed with brine, dried, and concentrated. The resulting residue was chromatographed on silica eluting with hexane/ethyl acetate 8:2 to give 2.45 g (50%) of the desired compound **10** as a yellow semi-solid: $[\alpha]_D^{20}$ +53.6 (*c* 4.4, $CHCl_3$); ^1H NMR (300 MHz) δ 9.29 (1H, s), 6.87 (1H, s), 6.68 (1H, s), 3.20 (1H, m), 2.84 (2H, m), 2.21 (1H, m), 1.26 (3H, d, *J*=9.0), 1.24 (3H, d, *J*=9.0), 1.23 (3H, s), 1.18 (3H, s); ^{13}C NMR (75 MHz) δ_C 206.8 (d), 151.0 (s), 146.9 (s), 132.2 (s), 126.7 (d), 126.3 (s), 110.7 (d), 49.8 (s), 42.7 (d), 37.6 (s), 36.1 (t), 31.8 (t), 28.9 (t), 26.6 (d), 24.9 (q), 22.5×2 (q), 21.5 (t), 17.6 (t), 13.9 (q); HRMS (ESI) *m*/*z* 301.2162 $[M+1]^+$, calcd for $C_{20}H_{29}O_2$: 301.2168.

*4.2.4. Synthesis of ferruginol (**1**). Method B.* A suspension of 18-oxoferruginol **10** (2.45 g, 8.1 mmol), KOH (85%, 1.6 g, 24.3 mmol), and hydrazine monohydrate (98%, 4 mL, 81 mmol) in diethyleneglycol (60 mL) is heated at 120 °C during 90 min. Then, the temperature is increased to 220 °C and maintained for 2 h 30 min. Then, the reaction mixture was cooled to rt and poured into 1 M HCl, extracted with ethyl acetate (3×30 mL), washed with brine, dried, and concentrated. The resulting residue (yellow oil) was chromatographed on silica eluting with hexane/ethyl acetate 5:1 to give 2.0 g (90%) of the desired compound **1** as yellowish oil with identical data to the sample obtained by method A.

Acknowledgements

Financial support from the Spanish Ministry of Science and Education, under a 'Ramón y Cajal' research grant, and also from the Generalitat Valenciana (project GV/2007/007) is gratefully acknowledged.

Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra for the new compound **9** and synthetic **10** and **1**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.09.055.

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