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Synthesis of nontrivial quinopimaric acid derivatives by oxidation with dimethyldioxirane

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ABSTRACT

Oxidation of dihydroquinopimaric acid methyl ester and its derivatives with dimethyldioxirane results in the formation of a nontrivial derivative and hemiacetals in high yields with excellent regioselectivity, as is demonstrated for an unsaturated diol. The structures of the products were confirmed by X-ray crystallographic analysis. Dihydroquinopimaric acid and its nontrivial derivative are found to be moderately active against influenza virus type A and the papilloma virus.

Abietane diterpenoids (e.g., abietic, dehydroabietic and levopimaric acids) are an important class of natural products which have been used as enantiomerically pure starting materials for the production of highly effective drugs, chiral reagents and polymers.[1–4] In particular, 12-sulfodehydroabietic acid monosodium salt (ecabet sodium) is an antiulcer drug,[5] which also inhibits the urease activity of *Helicobacter pylori*,[6] whereas a series of podocarpic acid amides were identified as liver X receptor agonists.[7]

Oxyfunctionalization of natural products is an effective method to obtain new biologically active compounds or their synthons.[8] Oxidative transformations of maleopimaric and fumaropimaric acids usually involve ozone or permanganate oxidation.[9] However, neither of these oxidation methods can be considered for preparative syntheses of oxyfunctionalized derivatives, particularly due to the *endo*-configuration of most Diels–Alder adducts which appears to complicate access to the double bond for common oxidizing agents. Moreover, oxidation of quinopimaric acid, except for some derivatives including dehydroquinopimaric acid,[10] has not been described. In this connection, the development of a method for the oxyfunctionalization of quinopimaric acid and its derivatives is highly desirable, especially in view of the recent findings that quinopimaric acid is a useful starting material for the synthesis of new anti-inflammatory, antiulcer and antiviral agents.[11–13]

As part of our ongoing programme on the synthesis of novel biologically active derivatives of levopimaric acid diene adducts, we report here the first example of an efficient oxidation of dihydroquinopimaric acid methyl ester **2**,[14a] its ether derivatives **5** and **6**[14b] and non-saturated diol **7**[14c] (Scheme 1). Good isolated yields and high selectivities were obtained with the powerful and versatile oxygen transfer reagent dimethyldioxirane (DMDO).[15]

Oxidation of compound **2** (pathway *f*, Scheme 1) was accomplished with four equiv of DMDO. This simple procedure involved addition of an aliquot of DMDO to the diterpenoid dissolved in acetone at room temperature. The reaction progress was monitored by TLC. Isolation of the product was carried out by solvent removal in vacuo, followed by crystallization of the residue from methanol. The ^{1}H and ^{13}C NMR spectra were in full agreement with structure **4** and the stereochemistry was confirmed by X-ray crystal analysis (Fig. 1).[16]

We propose the following mechanism to account for the formation of the compound **4** during the oxidation of dihydroquinopimaric acid methyl ester **2** with dimethyldioxirane (Scheme 2). This mechanism implies epoxidation of the double C13(14)[†] bond followed by epoxide ring opening to yield a hydroxy group at C14 and a double bond at C13(15). The hydroxy group is then involved in cyclization at C4.

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[†] Compounds are numbered in accordance with the Chemical Abstracts system, quinopimaric acid being a derivative of 1*H*-4b,12-ethenochrysene (see Ref. 14a).

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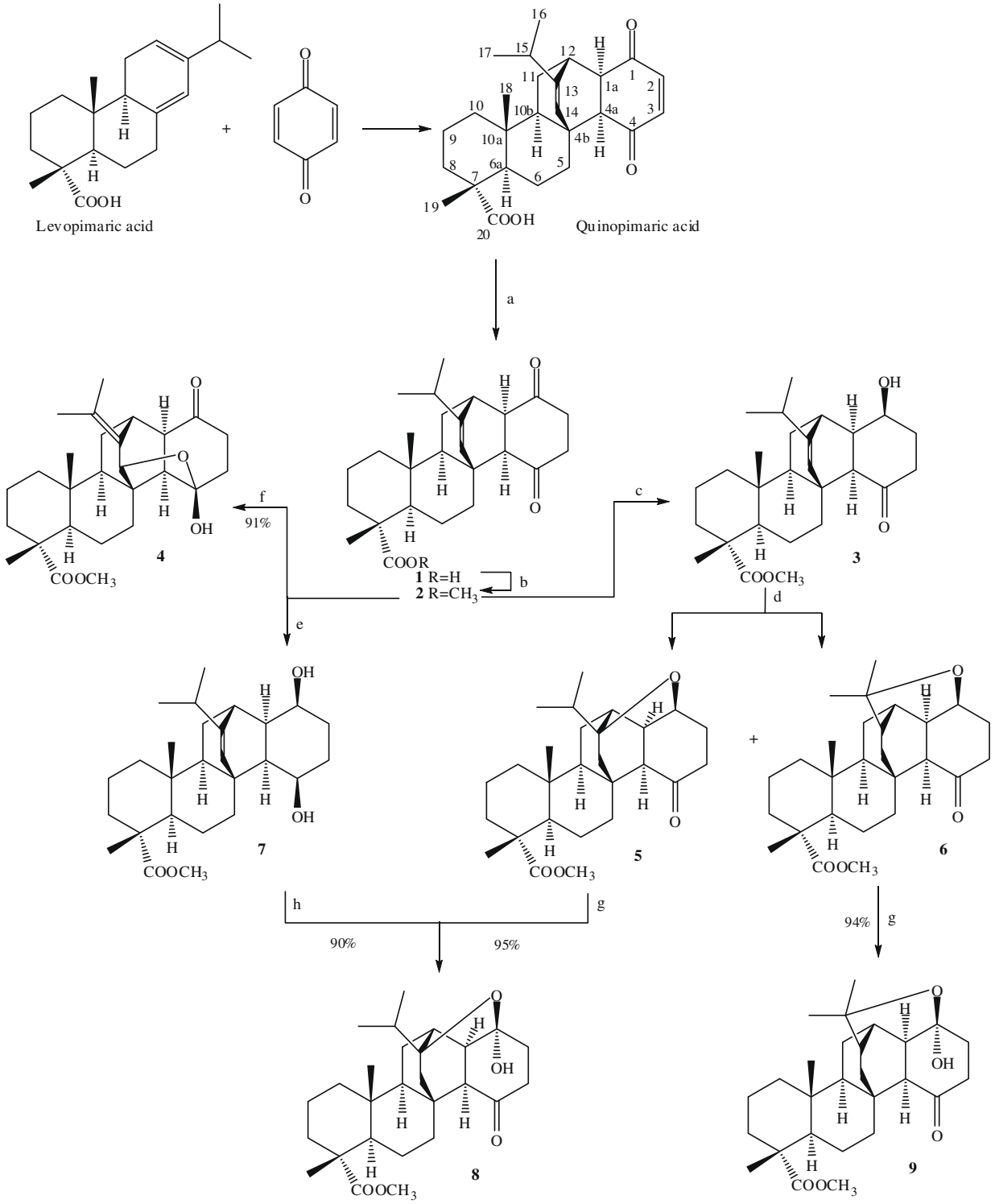


Scheme 1. Reagents and conditions: (a) Zn/AcOH, 100 °C; (b) CH_2N_2/Et_2O; (c) $NaBH_4$/MeOH, rt; (d) HCl/MeOH; (e) $NaBH_4$/EtOH, reflux; (f) 4 equiv DMDO, acetone, rt; (g) 1 equiv DMDO, acetone, rt; (h) 3 equiv DMDO, acetone, rt.

It is remarkable that the excess oxidant does not lead to oxidation of the C13(15) double bond of compound **4**. Moreover, this isopropenyl group remains intact even under treatment with ozone.

When ethers **5** and **6** were treated with DMDO, hemiacetals **8**[17]and **9**[18] were obtained in excellent yields (pathways *g*, Scheme 1). Formation of these compounds can be explained by oxygen insertion into the C(1)–H bond. In addition to identification by ^1H and ^{13}C NMR spectroscopy, the structure of **8** was also confirmed by X-ray crystallographic analysis (Fig. 2).[17]

Reaction of three equiv of DMDO with unsaturated diol **7** (pathway *h*, Scheme 1) was expected to result in the formation of a 1,4-diketo-13(14)-epoxide. However, the presence of an acidic environment apparently leads to regioselective formation of an ether bond at position –C(1)–O–C(13)–, in a manner similar to that described in our previous work,[14c] and oxidation of the hydroxy group at C4 to a ketone resulted in saturated hemiacetal **8**.

Dihydroquinopimaric acid (**1**) was found to be moderately active against influenza virus type A (H1N1) (EC_{50} 4.5; IC_{50} >100; SI

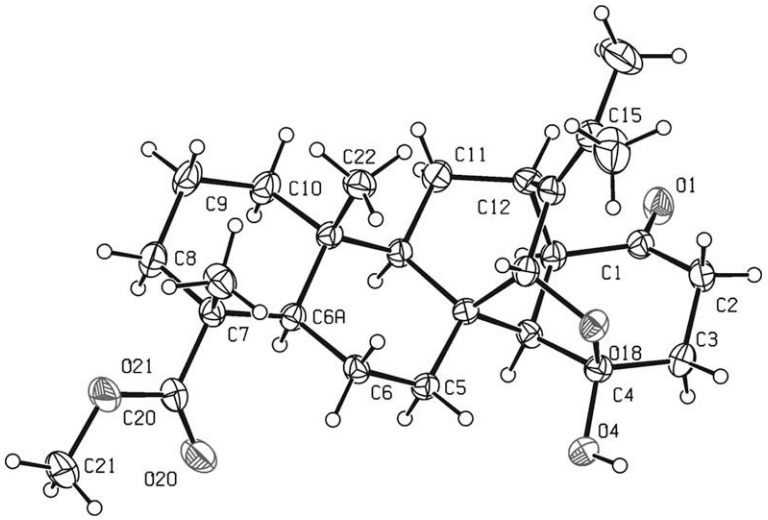
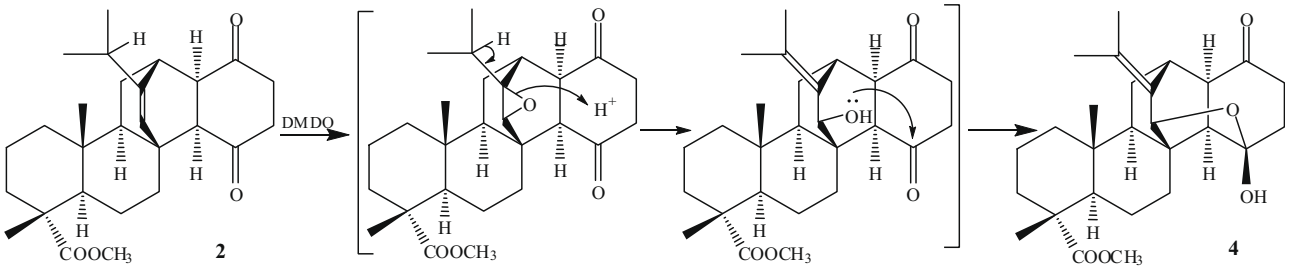


Figure 1. ORTEP plot of compound **4**. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented by circles of arbitrary size.



Scheme 2. Proposed mechanism for the oxidation of compound **2** to nontrivial derivative **4**.

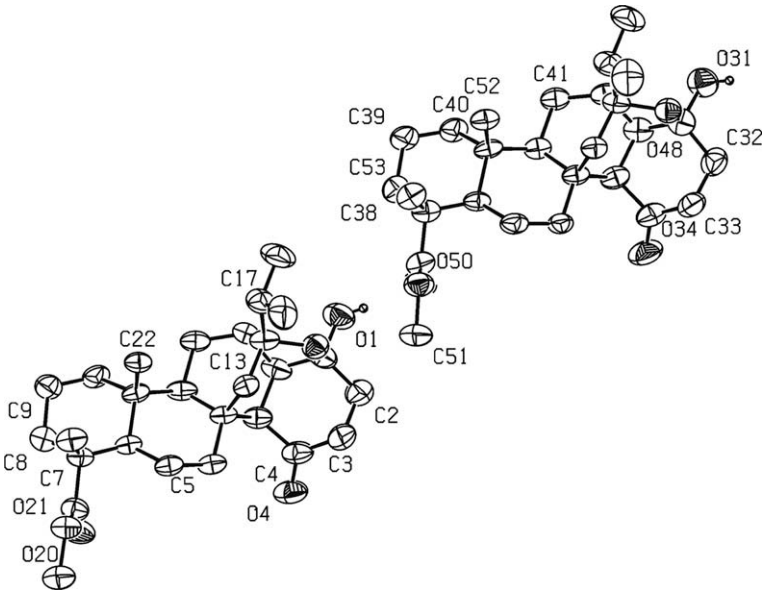


Figure 2. ORTEP plot of compound **8**. Displacement ellipsoids are drawn at the 50% probability level.

>22), whereas its nontrivial derivative **4** was shown to be moderately active against influenza virus type A (H1N1 and H3N2) (EC_{50} 3.2; IC_{50} >100; SI >31 and EC_{50} 2.6; IC_{50} >100; SI >38, respectively). Moreover, compounds **1** and **4** have demonstrated promising activity against papilloma virus (strain HPV-11; CC_{50} >50; EC_{50} <50; SI 30 and CC_{50} <25; EC_{50} <25; SI 20, respectively).[19]

In summary, a method for the synthesis of previously inaccessible nontrivial quinopimaric acid derivatives by oxidation with

dimethyldioxirane has been developed which has led to further successful oxidation of abietane diterpenoids.

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16. *4β-Hydroxy-4α,14α-epoxy-13(15)-ene-dihydroquinopimaric acid methyl ester* **4**: crystals from MeOH (mp 108–110 °C). $[\alpha]_D^{20}$ +21 (*c* 0.45, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.69 (s, 3H), 0.81–0.99 (m, 2H), 1.12 (s, 3H), 1.18–1.55 (m, 9H), 1.61 (d, *J* 6.91 Hz, 3H), 1.62–1.75 (m, 2H), 1.79 (d, *J* 6.91 Hz, 3H), 1.98–2.61 (m, 7H), 2.70–2.85 (m, 1H), 3.49 (br s, 1H), 3.65 (s, 3H), 4.80 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 212.8, 179.0, 132.5, 131.2, 101.5, 79.5, 55.2, 51.8, 51.7, 49.3, 47.0, 46.1, 45.6, 37.5, 37.3, 36.6, 36.0, 34.8, 34.7, 33.6, 30.8, 22.0, 19.9, 19.6, 17.3, 16.5, 13.7. *Crystallographic data* for **4**: the X-ray diffraction data were collected on a Bruker AXS Kappa Apex diffractometer at 296 K (graphite monochromator, CuK_α radiation (1.54184 Å). $C_{27}H_{38}O_5$, colourless prismatic crystal: 0.39 × 0.17 × 0.10 mm, M_r = 442.57 g mol^{-1}, monoclinic, $P2_1$, *a* = 12.892(7), *b* = 7.176(4), *c* = 13.703(7) Å, β = 115.673(6)°, *V* = 1142.5(11) Å^3, *Z* = 2, ρ_{calc} = 1.286 g cm^{-3}, $\mu(\lambda CuK_\alpha)$ = 0.87 cm^{-1}. *F*(0 0 0) = 480, reflections collected = 10296, unique = 5274, *R*(int) = 0.0523, full-matrix least-squares on F^2, parameters = 298. Final indices R_1 = 0.0592, wR_2 = 0.1318 for 2745 reflections with $I > 2\sigma(I)$; R_1 = 0.1338, wR_2 = 0.1733 for all data, goodness-of-fit on F^2 = 0.845, largest difference in peak and hole (0.234 and −0.180 e Å^{-3}). Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre (CCDC) as Supplementary Publication No. CCDC 704775 (http://www.ccdc.cam.ac.uk/products/csd/request/). Refinement using SHELXTL.
17. *1α-Hydroxy-1β,13-epoxydihydroquinopimaric acid methyl ester* **8**: crystals from MeOH (mp 192–194 °C). $[\alpha]_D^{20}$ +52 (*c* 1.35, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.91 (s, 3H), 0.97 (d, *J* 7.11 Hz, 3H), 0.99 (d, *J* 7.11 Hz, 3H), 1.09 (s, 3H), 1.11–1.85 (m, 12H), 1.99–2.30 (m, 6H), 2.41–2.53 (m, 5H), 2.65 (br s, 1H), 3.61 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 212.0, 178.9, 100.4, 86.6, 60.2, 55.3, 51.9, 51.8, 49.9, 47.9, 47.1, 43.0, 38.7, 38.6, 37.8, 36.4, 36.0, 35.7, 34.7, 34.0, 31.9, 21.0, 17.8, 16.9, 16.6, 16.4, 15.4. *Crystallographic data* for **8**: the X-ray diffraction data were collected on a Bruker AXS Smart Apex diffractometer at 296 K. $C_{27}H_{40}O_5$, colourless prismatic crystal: 0.036 × 0.089 × 0.434 mm, M_r = 444.59 g mol^{-1}, monoclinic, $P2_1$, *a* = 13.8927(14), *b* = 7.0253(7), *c* = 24.733(3) Å, β = 94.116(8)°, *V* = 2407.8(4) Å^3, *Z* = 4, ρ_{calc} = 1.226 g cm^{-3}, $\mu(\lambda MoK_\alpha$ 0.71073 Å) = 6.60 cm^{-1}. *F*(0 0 0) = 968, reflections collected = 13521, unique = 6815, *R*(int) = 0.1466, full-matrix least-squares on F^2, parameters = 588. Final indices R_1 = 0.0723, wR_2 = 0.1592 for 2658 reflections with $I > 2\sigma(I)$; R_1 = 0.1338, wR_2 = 0.2072 for all data, goodness-of-fit on F^2 = 0.836, largest difference in peak and hole (0.145 and −0.188 e Å^{-3}). Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 717983 (http://www.ccdc.cam.ac.uk/products/csd/request/). Refinement using SHELXTL.
18. *1α-Hydroxy-1β,15-epoxydihydroquinopimaric acid methyl ester* **9**: crystals from MeOH (mp 183–185 °C). $[\alpha]_D^{20}$ +3 (*c* 1.10; $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.90 (s, 3H), 0.96 (d, *J* 7.11 Hz, 3H), 0.98 (d, *J* 7.11 Hz, 3H), 1.07 (s, 3H), 1.13–1.87 (m, 12H), 1.95–2.25 (m, 6H), 2.40–2.51 (m, 5H), 2.63 (br s, 1H), 3.62 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 212.0, 179.1, 95.9, 75.5, 59.2, 55.0, 51.9, 50.2, 47.2, 40.0, 38.8, 38.4, 38.2, 37.6, 36.6, 36.0, 35.6, 31.9, 28.7, 27.7, 27.0, 26.0, 23.0, 21.2, 17.1, 16.4, 14.2. Calcd for $C_{27}H_{40}O_5$ (%): C, 72.94; H, 9.07. Found (%): C, 72.85; H, 9.10.
19. The protocols and explanations of the test results are available at the AACF website (www.niaid-aacf.org).