First Enantiospecific Synthesis of Antileishmanial 12-Deoxyroyleanone from Abietic Acid

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Abstract: 12-Deoxyroyleanone (**1**), an abietane diterpenoid with appreciable antileishmanial activity, has been efficiently synthesized from abietic acid (**10**; 11 steps for a 25% overall yield).

Key words: enantiospecific synthesis, diterpenoids, antileishmanial activity

In recent years, the isolation of a wide variety of abietane diterpenes with various biological activities, e.g. antiviral,[1] antibiotic,[1b,2] antimalarial,[3] antioxidant,[4] antitumor[5] and antileishmanial,[6] has been reported.

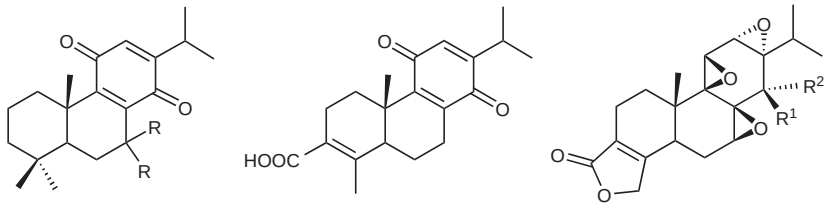
Noteworthy among these, because of their remarkable and potent activities, is a number of variously oxidized compounds bearing an oxygenated function on C-14. Representative examples of the latter are 12-deoxyroyleanone (**1**), an antileishmanial agent,[6] and cryptoquinone (**2**), which shows cytotoxic activity against mouse lymphoid neoplasm (P388) cells.[7] Other interesting related compounds include tryptoquinone A (**3**), a promising agent for treatment of rheumatoid arthritis,[8] and triptonide (**4**) and triptolide (**5**), which have potent antitumor,[9] anti-inflammatory,[10] immunosuppressive[10b,11] and antifertility activities[10b,12] (Figure 1).

Despite the evident interest of these metabolites, few syntheses have been reported, most of them being total syntheses involving Diels–Alder cycloaddition,[13] Robinson annulation,[8] electrophilic cyclizations[14] and radical cyclizations.[15] A synthesis of **5** from dehidroabietic acid has been reported by van Tamelen;[16] 14-hydroxydehydroabietic acid, the key intermediate in the synthetic sequence, being prepared by electrophilic substitution via the corresponding diazonium salt.[17]

Following our research into the synthesis of natural bioactive compounds based on homochiral synthons obtained from natural sources,[18] we are developing a route to this type of compound starting from abietic acid (**10**).

As noted above, our initial objective was to devise an efficient synthesis of the key 14-hydroxyabietic acid, or related compounds such as **6**, from abietic acid (**10**). The procedure previously reported involving nitration of the aromatic ring and further transformation of the nitro group into the hydroxyl group[17] proved to be unsuitable because of its length and low regioselectivity. Thus, we planned an alternative method to prepare ester **6** directly from **10**, as depicted in the retrosynthetic Scheme 1. Compound **6** is obtained after aromatization of the methyl 14-methoxyabietate (**7**), resulting from the dehydration of monomethylether **9**, derived from the 13,14-diol **8**, which can be synthesized by regioselective dihydroxylation of abietic acid (**10**).[19]

Scheme 2 shows the complete sequence from **10** to **6**. Abietic acid (**10**) was efficiently converted into diol **11**, by means of a procedure improved from that reported in the literature. After esterification of the carboxylic acid, the secondary hydroxyl group was methylated, affording **9**, which underwent regioselective dehydration by treating



1 R, R: H
2 R, R: =O

3

4 R^1, R^2: =O
5 R^1: H; R^2: OH

Figure 1

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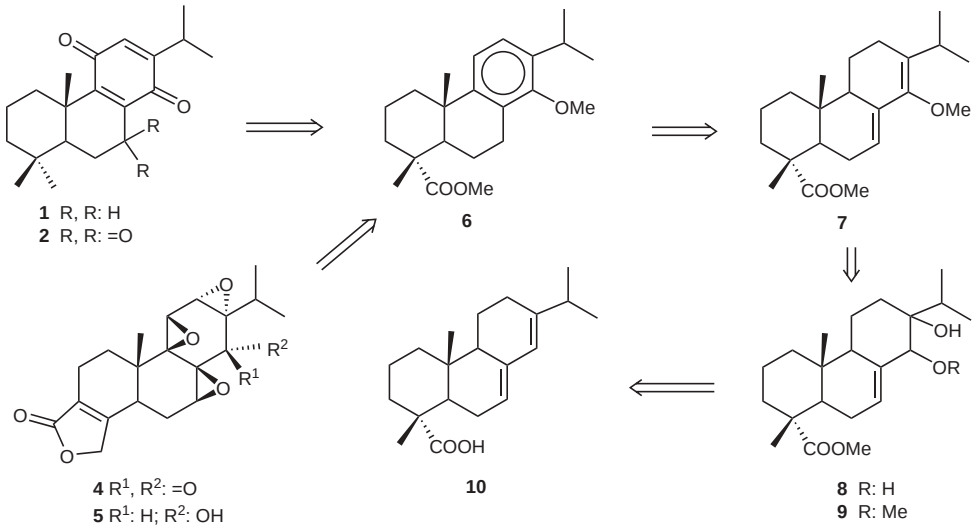
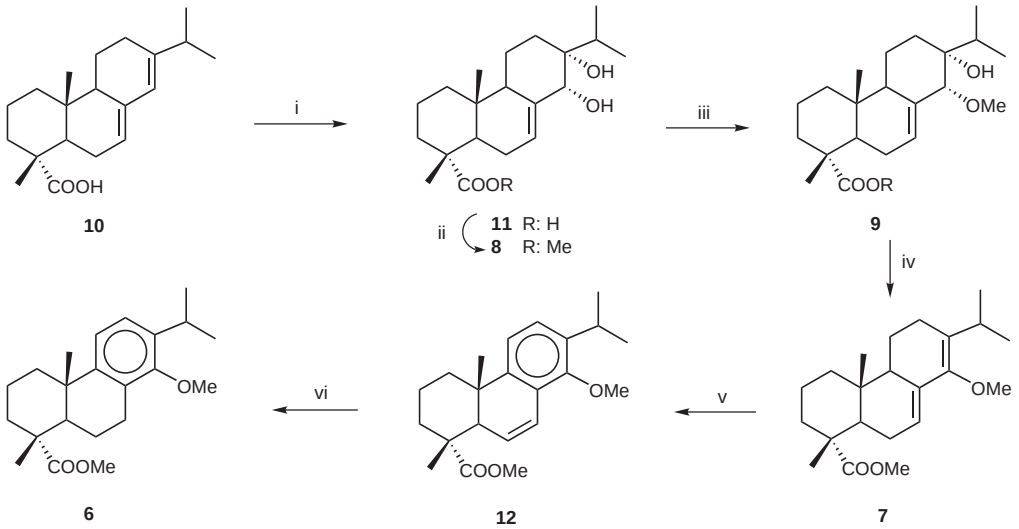


Scheme 1



Scheme 2 (i) ac. OsO_4 0.2%, Me_3NO, pyridine, *t*-BuOH, Ar, reflux, 7 d; (ii) MeI, K_2CO_3, acetone, reflux, 24 h (90% from **10**); (iii) NaH, THF, MeI, 0 °C, 2 h (96%); (iv) $SOCl_2$, Et_3N, CH_2Cl_2, –78 °C, 20 min (74%); (v) Br_2, CCl_4, $CaCO_3$, reflux, 12 h (70%); (vi) H_2, Pd/C, MeOH, r.t., 3 h (96%).

with thionyl chloride and triethylamine. The resulting methoxydiene **7** was then transformed into the dehydroabietic acid derivative **12** by treatment with bromine in carbon tetrachloride under reflux. Hydrogenation of **12** under conventional conditions gave methyl 14-methoxydehydroabietate (**6**).

Ester **6** is a suitable precursor of bioactive metabolites such as **1**–**5**, and so we synthesized 12-deoxyroyleanone (**1**) starting from **6** (Scheme 3). First, the methoxycarbonyl was transformed into the methyl group. Treatment of **6** with lithium aluminum hydride gave alcohol **13**, which was oxidized to aldehyde **14** and this converted into **15** under the Wolff–Kishner conditions. An alternative transformation of **13** into **15**, via the mesyl derivative **16**, was investigated. When **16** was treated with lithium aluminum hydride, **13** was regenerated; nevertheless, **15** was obtained by treating **16** with zinc and sodium iodide.[20] Deprotection of methylether with boron tribromide lead to phenol **17**,[21] which was finally converted into **1** after treatment with potassium nitrosodisulfonate.

In summary, a short and efficient procedure to prepare key intermediate **6** from abietic acid (**10**) has been developed. The antileishmanial 12-deoxyroyleanone (**1**) was synthesized starting from compound **6**.

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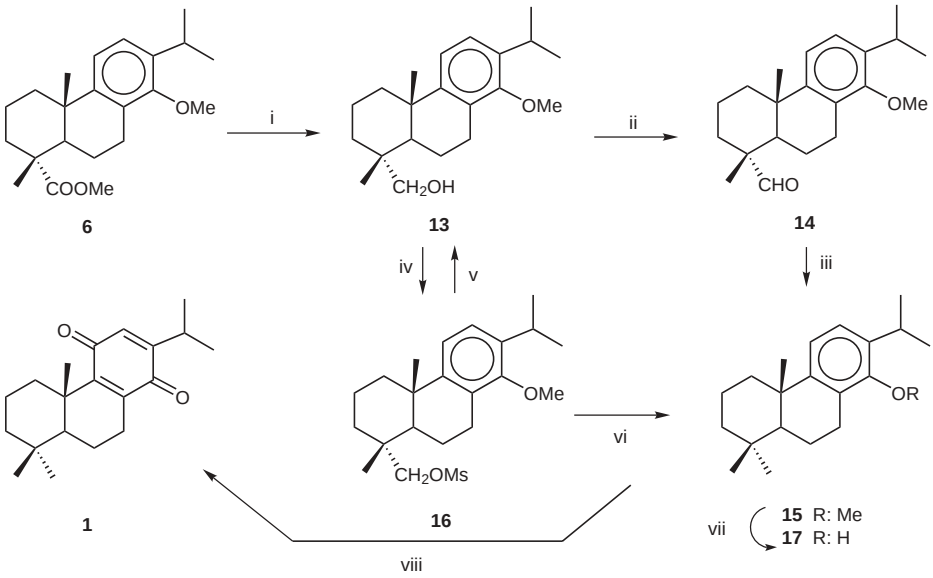

Scheme 3 (i) $LiAlH_4$, THF, r.t., 3 h (95%); (ii) PCC, CH_2Cl_2, r.t., 1 h (70%); (iii) NH_2NH_2, KOH, ethyleneglycol–ethyleneglycol dimethyl-ether 3:2, 180 °C, 3 d (70%); (iv) MsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 4 h (93%); (v) $LiAlH_4$, THF, reflux, 24 h (95%); (vi) Zn, NaI, HMPA, 110 °C, 3 d (75%); (vii) BBr_3, CH_2Cl_2, –10 °C, 30 min (95%); (viii) $(KSO_3)_2NO$, MeOH, r.t., 4 h (91%).

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(21) All new compounds were fully characterized spectroscopically and had satisfactory HRMS data. Selected data: **Compound 6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (6 H, d, *J* = 6.9 Hz), 1.23 (3 H, s), 1.40–1.60 (m, 2 H), 1.60–1.95 (m, 5 H), 2.24 (1 H, dd, *J* = 12.5, 2.0 Hz), 2.30 (1 H, br d, *J* = 12.7 Hz), 2.79 (1 H, ddd, *J* = 17.6, 11.3, 6.2 Hz), 2.99 (1 H, dd, *J* = 17.6, 6.2 Hz), 3.34 (1 H, h, *J* = 6.9 Hz), 3.67 (3 H, s), 3.73 (3 H, s), 7.02 (1 H, d, *J* = 8.1 Hz), 7.10 (1 H, d, *J* = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.5 (CH_3), 18.6 (CH_2), 21.3 (CH_2), 23.8 (CH_3), 23.9 (CH_3), 24.5 (CH_3), 25.1 (CH_3), 26.0 (CH), 36.6 (CH_3), 37.1 (C), 38.1 (CH_2), 44.6 (CH), 47.6 (C), 51.9 CH_3), 60.4 (CH_3), 120.2 (CH), 123.8 (CH), 128.4 (C), 138.0 (C), 148.5 (C), 154.8 (C), 179.0 (C).

Compound 7: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (3 H, s), 0.95 (3 H, d, *J* = 6.9 Hz), 0.98 (3 H, d, *J* = 6.9 Hz), 1.14 (1 H, dd, *J* = 12.5, 4.9 Hz), 1.26 (3 H, s), 1.40–2.20 (13 H, m), 3.11 (1 H, h, *J* = 6.9 Hz), 3.52 (3 H, s), 3.64 (3 H, s), 5.74 (1 H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 17.0 (CH_3), 18.2 (CH_2), 20.5 (CH_3), 20.7 (CH_3), 22.4 (CH_2), 22.7 (CH_2), 25.5 (CH_2), 26.8 (CH), 34.8 (C), 37.0 (CH_2), 38.5 (CH_2), 44.8 (CH), 46.6 (C), 51.5 (CH), 51.9 (CH_3), 60.5 (CH_3), 117.1 (CH), 130.5 (C), 130.7 (C), 147.8 (C), 179.1 (C).

Compound 9: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (3 H, s), 0.85 (3 H, d, *J* = 6.9 Hz), 0.89 (3 H, d, *J* = 6.9 Hz), 1.22 (3 H, s), 2.05 (1 H, h, *J* = 6.9 Hz), 3.42 (3 H, s), 3.44 (1 H, br s), 3.60 (3 H, s), 5.66 (1 H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.6 (CH_3), 16.5 (CH_3), 17.5 (CH_3), 18.0 (CH_2), 18.2 (CH_3), 19.5 (CH_2), 25.0 (CH_2), 26.6 (CH_2), 33.4 (CH), 35.3 (C), 37.1 (CH_2), 39.3 (CH_2), 44.9 (CH), 46.5 (C), 51.3 (CH), 51.9 (CH_3), 60.2 (CH_3), 76.3 (C), 83.5 (C), 120.0 (CH), 134.8 (C), 179.3 (C).

Compound 12: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (3 H, s), 1.19 (6 H, d, *J* = 6.9 Hz), 1.38 (3 H, s), 1.60–1.85 (4 H, m), 2.14 (2 H, m), 2.88 (1 H, dd, *J* = 3.1, 2.8 Hz), 3.28 (1 H, h, *J* = 6.9 Hz), 3.63 (3 H, s), 3.70 (3 H, s), 5.76 (1 H, dd, *J* = 9.8, 2.8 Hz), 6.78 (1 H, dd, *J* = 9.8, 3.1 Hz), 6.90 (1 H, d, *J* = 8.1 Hz), 7.08 (1 H, d, *J* = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9 (CH_3), 18.5 (CH_2), 20.7 (CH_3), 23.9 (CH_3), 24.0 (CH_3), 26.2 (CH), 35.6 (CH_2), 35.7 (CH_2), 37.5 (C), 44.7 (C), 46.4 (CH), 52.0 (CH_3), 62.3 (CH_3), 117.8 (CH), 122.6 (CH), 125.7 (CH), 125.7 (C), 129.8 (CH), 139.0 (C), 146.9 (C), 153.4 (C), 178.5 (C).

Compound 15: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (3 H, s), 0.96 (3 H, s), 1.18 (3 H, s), 1.21 (3 H, d, *J* = 6.8 Hz), 1.20 (3 H, d, *J* = 6.8 Hz), 1.32 (1 H, dd, *J* = 12.5, 2.1 Hz), 1.39 (1 H, dt, *J* = 13.1, 3.6 Hz), 1.48 (1 H, br d, *J* = 13.1 Hz), 1.55–1.85 (8 H, m), 1.93 (1 H, dd, *J* = 13.2, 7.8 Hz), 2.26 (1 H, br d, *J* = 12.7 Hz), 2.73 (1 H, ddd, *J* = 17.7, 11.4, 7.7 Hz), 3.01 (1 H, dd, *J* = 17.6, 7.7 Hz), 3.28 (1 H, h, *J* = 6.9 Hz), 3.72 (3 H, s), 7.02 (1 H, d, *J* = 8.4 Hz), 7.05 (1 H, d, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.7 (CH_2), 19.4 (CH_2), 21.7 (CH_3), 24.0 (CH_3), 23.4 (CH_3), 25.0 (CH_3), 29.5 (CH_2), 26.1 (CH), 33.4 (CH_3), 33.4 (C), 37.8 (C), 39.0 (CH_2), 41.7 (CH_2), 50.2 (CH), 60.5 (CH_3), 120.4 (CH), 123.7 (CH), 128.7 (C), 137.8 (C), 149.4 (C), 154.0 (C).

Compound 17: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (3 H, s), 0.95 (3 H, s), 1.18 (3 H, s), 1.24 (6 H, d, *J* = 6.8 Hz), 1.95 (1 H, m), 2.26 (1 H, br d, *J* = 12.7 Hz), 2.60 (1 H, ddd, *J* = 16.5, 11.5, 6.2 Hz), 2.80 (1 H, dd, *J* = 16.5, 6.2 Hz), 3.14 (1 H, h, *J* = 6.8 Hz), 4.50 (1 H, s), 6.85 (1 H, d, *J* = 8.2 Hz), 7.01 (1 H, d, *J* = 8.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5 (CH_2), 19.4 (CH_2), 21.7 (CH_3), 22.6 (CH_3), 22.9 (CH_3), 24.4 (CH_3), 24.9 (CH_3), 26.9 (CH), 33.4 (CH_3), 33.4 (C), 38.8 (C), 39.0 (CH_2), 41.7 (CH_2), 49.8 (CH), 116.5 (CH), 123.3 (CH), 130.9 (C), 130.9 (C), 149.1 (C), 150.3 (C).