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Synthesis of 12-deoxyroyleanone, cryptoquinone, 11,14-dihydroxy-8,11,13-abietatrien-7-one, and related derivatives from dehydroabietic acid

Yoh-ichi Matsushita,* Yoshihisa Iwakiri, Satoru Yoshida, Kazuhiro Sugamoto and Takanao Matsui

Faculty of Engineering, University of Miyazaki, Gakuen-Kibanadai, Miyazaki 889-2192, Japan

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Abstract—Naturally occurring abietane quinones and hydroquinone, namely, 12-deoxyroyleanone (**1a**), cryptoquinone (**4a**), and 11,14-dihydroxyabieta-8,11,13-trien-7-one (**5a**), together with the epimers of tryptoquinones D (**2**) and F (**3**), were first synthesized from dehydroabietic acid (**6**).

12-Deoxyroyleanone (**1a**) was newly isolated from *Salvia cilicica*, which exhibited potent inhibitory activity against the amastigote forms of *Leishmanial donovani* and *L. major* (Fig. 1).[1] Tryptoquinones D (**2**) and F (**3**) were isolated from the stems of *Tripterygium wilfordii* var. *regelii* and had potent inhibitory activities against the release of interleukin-1α and -1β for human cells.[2] Cryptoquinone (**4a**) was isolated from the bark of *Cryptomeria japonica* and showed antifungal activities against *Pyricularia orizae* and *Alternaria alternata* and cytotoxic activity against mouse lymphoid (P388) cells.[3] 11,14-Dihydroxy-8,11,13-abietatrien-7-one (**5a**) was found from the heartwood of *Chamaecyparis obtus*.[4] It seems to be important to develop synthetic routes of these new abietane quinones and related derivatives for elucidation of the relationship between their structures and promising activities.

Although several syntheses of abietane quinones and hydroquinones bearing an oxygen function at C-12 position, for example, royleanone, 7-oxoroyleanone, cyptojaponol, and hyptol, have been reported from abietic acid (**6**),[5–8] few syntheses of abietane quinones having no oxygen function at the C-12 position, namely, 8,12-abietadien-11,14-dione derivatives were reported.

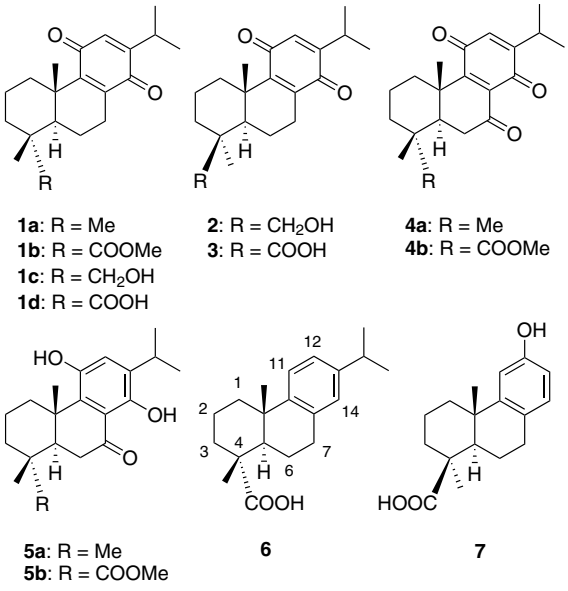

Figure 1.

The 8,11,13-abietatriene derivatives bearing alkoxy or hydroxy group(s) at the C-11 position or both C-11 and C-14 positions have been only accomplished by reconstruction of the B-ring lactones, which were prepared from 8,11,13-abietatrien-7-one derivatives by the Baeyer–Villiger oxidation, via the Friedel–Craft acylation.[9–12] Cambie et al. recently improved this synthetic

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* Corresponding author. Tel.: +81 985 58 7389; fax: +81 985 58 7323; e-mail: matusita@cc.miyazaki-u.ac.jp

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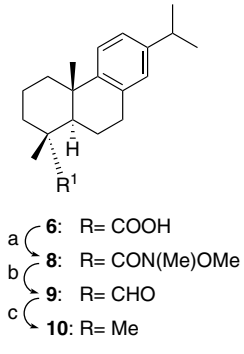
route and synthesized the quinones **2** and **3** from podocarpic acid (**7**) in 12 steps via the Fries rearrangement of the intermediary lactone.[13] However, these synthetic methods require longer steps due to the re-construction of the B-ring. Therefore, we investigated a new synthetic route of the 8,12-abietadien-11,14-dione derivatives from 14-hydroxy-8,11,13-abietatriene derivatives in expectation of reduction in synthetic steps. We herein report a first synthesis of the quinones **1a** and **4a**, the hydroquinone **5a**, and related derivatives **1b–d**, **4b**, and **5b** from **6**.

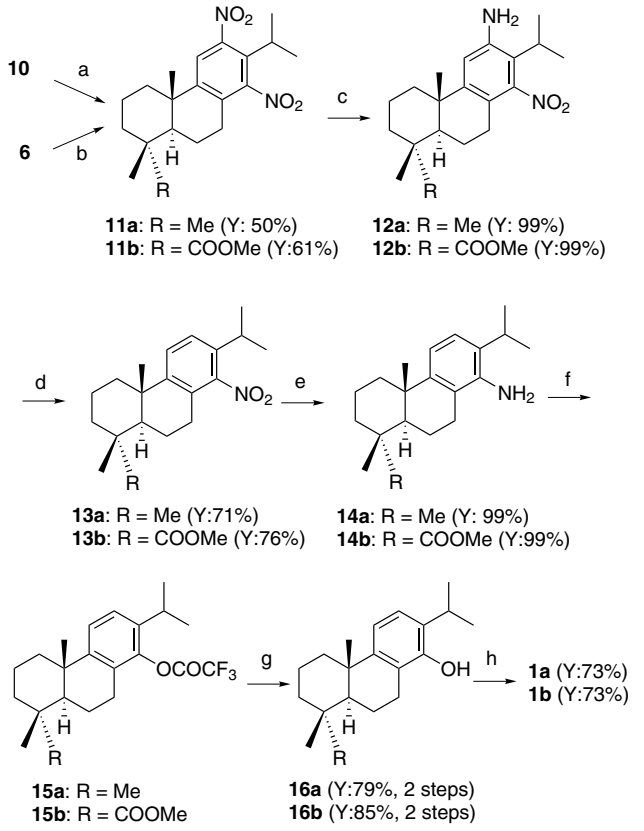
Treatment of **6** with thionyl chloride gave acid chloride, which was allowed to react with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of Et_3N in refluxing THF to afford crude amide **8** (Scheme 1). Reduction of **8** with $LiAlH_4$ in ether at −10 °C gave crude aldehyde **9**, which was reduced under the Wolff–Kishner reduction conditions to produce 8,11,13-abietatriene (**10**) in 68% yield from **6**. Although the preparation of **9** has been generally achieved via reduction of **6** with LAH followed by oxidation with CrO_3 in pyridine,[14] the present procedure has the advantage of permitting no use of noxious CrO_3 in large-scale preparation.

Many efforts have been made toward nitration of 8,11,13-abietatriene derivatives.[15–22] Mononitration of **10** was known to occur under mild conditions but resulted in formation of a mixture of 12-nitro and 14-nitro compounds in ratio of 3:1–1:1.[15–17]

14-Hydroxy-8,11,13-abietatriene derivatives have been synthesized via nitration of 8,11,13-abietatrien-7-one derivatives at the C-14 position.[19–23] However, the nitration of the abietatrienones has a demerit of producing a mixture of 14-nitro and 13-nitro compounds in ratio of ca. 1:1.[19,20,22] Therefore, a synthetic route of **1a**,**b** via selective removal of 14-nitro substituent from 12,14-dinitro compounds was newly developed (Scheme 2). Nitration of **10** with 64% HNO_3–95% H_2SO_4 gave dinitro compound **11a**, and nitration of **6** under the same conditions as used for **10** followed by treatment with CH_2N_2 gave dinitro ester **11b**.[21,25] Thus obtained compounds **11a**,**b** were reduced selectively with $HCOONH_4$ in the presence of Pd/C as a catalyst,[26,27] to afford 12-amino-14-nitro compounds **12a**,**b**. Among several methods for deamination by diazotization–reduction,[28–33] the treatment of **12a**,**b** with *i*-amyl nitrite in refluxing dioxane[33] afforded 14-nitro compounds **13a**,**b** in the best yields, which were reduced with $HCOONH_4$–Pd/C to 14-amino compounds **14a**,**b**. Arenediazonium salts prepared from arylamines have been usually decomposed with hot protic solvents such as water, alcohols, and acetic acid.[22–24,34–38] In this work, it was found that in situ diazotization–decomposition of **14a**,**b** in trifluoroacetic acid (TFA) successfully proceeded at room temperature to afford crude 14-trifluoroacetoxy compounds **15a**,**b** in high yields. Without further purification, the crude **15a**,**b** were converted into 14-hydroxy compounds **16a**,**b**. The oxidation of **16a**,**b** with 30% H_2O_2 catalyzed by $RuCl_3$[39] gave the abietane quinones **1a** and **1b**: their respective yields from **10** and **6** were 20% and 28% yields in seven steps. Physical and spectral data of synthetic **1a** were consistent with those reported for natural **1a**: mp 83.8–84.8 °C, $[\alpha]_D^{20}$ −65.3 (*c* 0.407, MeOH); lit.[1] $[\alpha]_D^{20}$ −60.0 (*c* 0.05, MeOH), and no description of the melting point of natural **1a**.



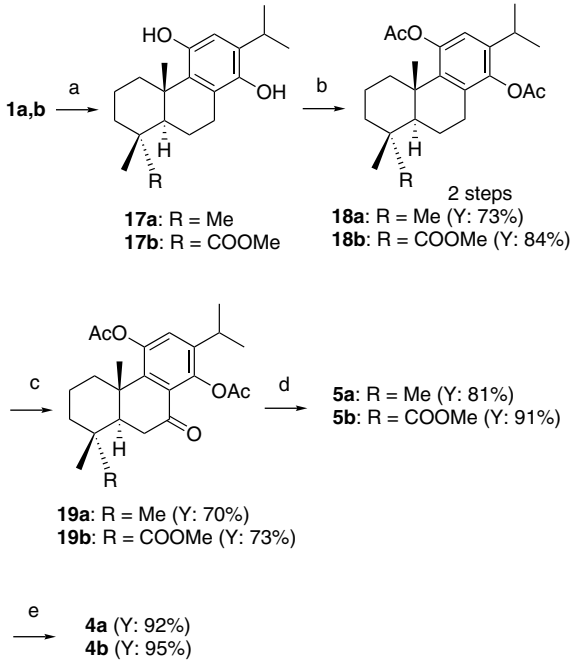
Scheme 1. Reagents and conditions: (a) $SOCl_2$ (3.0 equiv), cat. DMF, toluene, 90 °C, 3 h, then $NH_2OH{\cdot}HCl$ (1.5 equiv), Et_3N (4.0 equiv), THF, reflux, 2 d; (b) $LiAlH_4$ (1.2 equiv), −10 °C, 20 min; (c) $N_2H_4{\cdot}H_2O$ (6.0 equiv), KOH (5.0 equiv), $HO(CH_2)_2O(CH_2)_2OH$, 210 °C, 2 h (Y: 68% from **6**); (d) excess CH_2N_2, MeOH–Et_2O (Y: 93%).



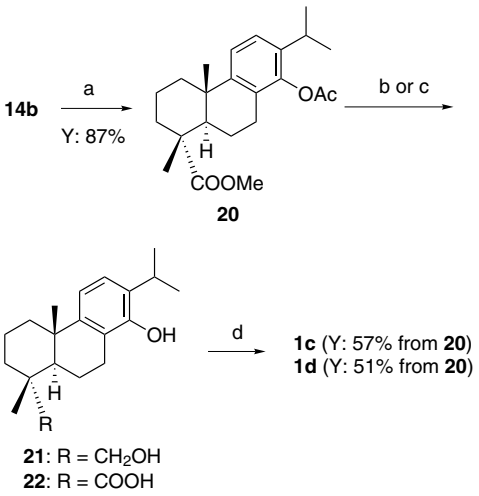
Scheme 2. Reagents and conditions: (a) 65% HNO_3 (25 equiv), 95% H_2SO_4 (47 equiv), 0 °C then rt, 0.5 h; (b) 65% HNO_3 (17 equiv), 95% H_2SO_4 (32 equiv), 0 °C then rt, 0.5 h; excess CH_2N_2, Et_2O, rt; (c) $HCOONH_4$ (8.5 equiv for **11a** and 3.5 equiv for **11b**), 10% Pd–C (1.0 wt equiv), CH_2Cl_2–MeOH, rt, 6.5 h for **11a** and 0.5 h for **11b**, under N_2; (d) *i*-amylONO (2.0 equiv), dioxane, reflux, 1.5 h; (e) $HCOONH_4$ (18 equiv), 10% Pd–C (1.0 wt equiv), CH_2Cl_2–MeOH, rt, 10 h for **13a** and 6 h for **13b**, under N_2; (f) *i*-amylONO (1.8 equiv for **14a** and 1.2 equiv for **14b**), CF_3COOH, 0 °C, 10 min then rt, 2 h for **14a** and 1 h for **14b**; (g) 2 M K_2CO_3 (1.2 equiv), MeOH, rt, 1.5 h; (h) 30% H_2O_2 (4.0 equiv for **16a** and 6.0 equiv for **16b**), $RuCl_3{\cdot}3H_2O$ (0.1 equiv), AcOH, 10–15 °C then rt, 2 h for **16a** and rt, 5 h for **16b**.

For synthesis of **4a**,**b**, attempts of direct oxidation of **1a**,**b** by oxidants such as pyridinium chlorochromate (PCC), CrO_3–Ac_2O–AcOH, and MnO_2 failed with recovered **1a**,**b** and/or complex reaction mixture. Synthesis of **4a**,**b** was achieved via conversion of **1a**,**b** into hydroquinones **17a**,**b** by $NaBH_4$ reduction as shown in Scheme 3. After acetylation of **17a**,**b**, 11,14-diacetoxy compounds **18a**,**b** were oxidized by the combined use of CrO_3 and acetic anhydride in acetic acid and benzene gave 7-oxo compounds **19a**,**b**, which were hydrolyzed by concd HCl in MeOH to afford the hydroquinones **5a**,**b**. Spectral data of **5a** were completely coincided with those reported for synthetic **5a**, though its melting point was high and specific rotation value was somewhat large compared with those reported: mp 225.1–226.3 °C, $[\alpha]_D^{25}$ +75.4 (*c* 0.371, $CHCl_3$); lit.[4] mp 178–179 °C, $[\alpha]_D^{24}$ +65.8 (*c* 0.37, $CHCl_3$). The hydroquinones **5a**,**b** were oxidized with MnO_2, to afford the quinones **4a**,**b**. Physical and spectral data of synthetic **4a** were consistent with those reported for natural **4a**: mp 107.3–108.2 °C, $[\alpha]_D^{25}$ −661.1 (*c* 0.338, $CHCl_3$); lit.[3] mp 105–106 °C, $[\alpha]_D^{25}$ −680 (*c* 0.1, $CHCl_3$).

The diazotization–decomposition of amino compound **14b** using acetic acid instead of TFA under the similar conditions described above gave 14-acetoxy compound **20** in high yield (Scheme 4). Reduction of **20** with $LiAlH_4$ afforded 14,18-diol **21** and hydrolysis of **20** with excess of 5 M NaOH followed by neutralization gave 14-hydroxy acid **22**. The epimers **1c** and **1d** of tryptoquinones D (**2**) and F (**3**) were synthesized from **21** and **22**, respectively, by the $RuCl_3$-catalyzed oxidation with



Scheme 3. Reagents and conditions: (a) $NaBH_4$ (8.0 equiv), MeOH, 0 °C, 10 min then rt 1 h, under N_2; (b) Ac_2O (8.0 equiv), DMAP (0.2 equiv), 0 °C then rt, 22 h for **17a** and 18 h for **17b**, under N_2; (c) CrO_3 (3.0 equiv), AcOH, 10–15 °C then rt, 5 h for **18a**; CrO_3 (5.0 equiv), Ac_2O (13 equiv), AcOH–benzene, 0 °C, 10 min then rt, 0.5 h for **18b**; (d) concd HCl, MeOH, reflux, 4 h, under N_2; (e) MnO_2, (1.2 wt equiv), CH_2Cl_2, rt 1 h.



Scheme 4. Reagents and conditions: (a) *i*-amylONO (1.2 equiv), AcOH, 5–10 °C, 10 min then rt, 1.5 h; (b) $LiAlH_4$ (8.0 equiv), Et_2O, 0 °C then rt, 4 h, under N_2 (to afford **21**); (c) excess 5 M NaOH, EtOH, reflux, 12 h, under N_2 (to afford **22**); (d) 30% H_2O_2 (4.0 equiv), $RuCl_3 \cdot 3H_2O$ (0.1 equiv), AcOH, 5–15 °C, 10 min then rt, 2 h.

H_2O_2: Their respective yields from **6** were 23% and 20% in seven steps.

In conclusion, a first and short-steps synthesis of 12-deoxyryleanone (**1a**), cryptoquinone (**4a**), and 11,14-dihydroxy-8,11,13-abietatrien-7-one (**5a**) together with related derivatives has been achieved from dehydroabietic acid (**6**). Antimicrobial activities of these quinones and related derivatives is currently evaluated in our laboratory.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.03.170.

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