Thermal rearrangement of harunganin and allylations of some compounds from *Harungana madagascariensis*

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In honor of Prof. Dr. B. M. Abegaz on the occasion of his 60th birthday anniversary

Abstract

The thermal rearrangement of harunganin (**1**), a major constituent of *Harungana madagascariensis*, was investigated. The rearranged products are mostly found as natural constituents in this plant. In addition, allylations of some anthranoids including harunganin (**1**), harongin anthrone (**8**), harunganol B (**9**), kenganthranol A (**10**) and 1,7-dihydroxyxanthone (**14**) with allyl bromide in the presence of potassium carbonate were studied. The chelated phenolic hydroxyl groups were not allylated under theses conditions. Harongin anthrone (**8**) and harunganol B (**9**) gave the *O*- and *C*-bisallylation products **11** and **12**, respectively.

Keywords: *Harungana madagascariensis*, thermal rearrangement, allylation, harunganin, anthrones, xanthone

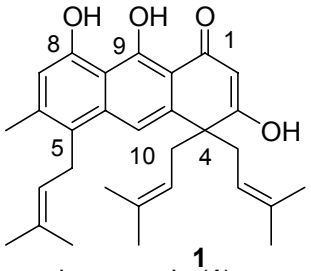
Introduction

Several prenylated anthranoids have been found to occur in the family Hypericaceae and the majority of them are *C*-prenylated. *Harungana madagascariensis* from this family is recognized to be a particularly rich source of this type of secondary metabolites.[1-4] Harunganin (**1**), harongin

anthrone (**8**), harunganol B **(9**), kenganthranol A (**10**) and 1,7-dihydroxyxanthone (**14**) have been isolated from the stem bark of this plant and their structures were elucidated by means of spectroscopic analysis.[1-4] Apart from the last compound, all were *C*-prenylated and showed strong α-glucosidase enzyme inhibition activity.[3,4] Harunganin [(3,8,9-trihydroxy-6-methyl-4,4,5-tris(3-methylbut-2-enyl)anthracen-1(4H)-one] (**1**), the major constituent of this plant and the most active in this series, was observed to be instable in solution. The thermal (neat) rearrangement of harunganin methyl ether was studied by Richtie and Talyor[2] and that of harunganin (**1**) and the related isomers ferruginin A and B by Monache et al.[5] However, in the previous work[2], only one rearranged product was observed upon heating of harunganin methyl ether whereas several products were formed according to our TLC studies in the solution decomposition of harunganin (**1**). Therefore, in the course of the present study, we reinvestigated the thermal rearrangement of harunganin (**1**) in dichloromethane solution. In addition, we included the *O*-allylation of this and some other natural phenolic compounds from this plant as model studies, using an allylation method described in the literature.[6-9]

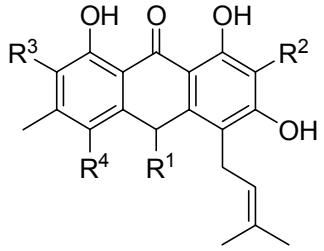
Results and Discussion

Refluxing of harunganin (**1**) in dichloromethane gave a mixture of five rearranged compounds **2**-**6**. As can be seen from Scheme 1, the sterically congested two prenyl groups at C-4 thermally rearrange into the *ortho* or *para* position of the respective phenolic hydroxyl groups at C-3, C-8, and C-9.



1
harunganin (**1**)

CH_2Cl_2
reflux, 90 h



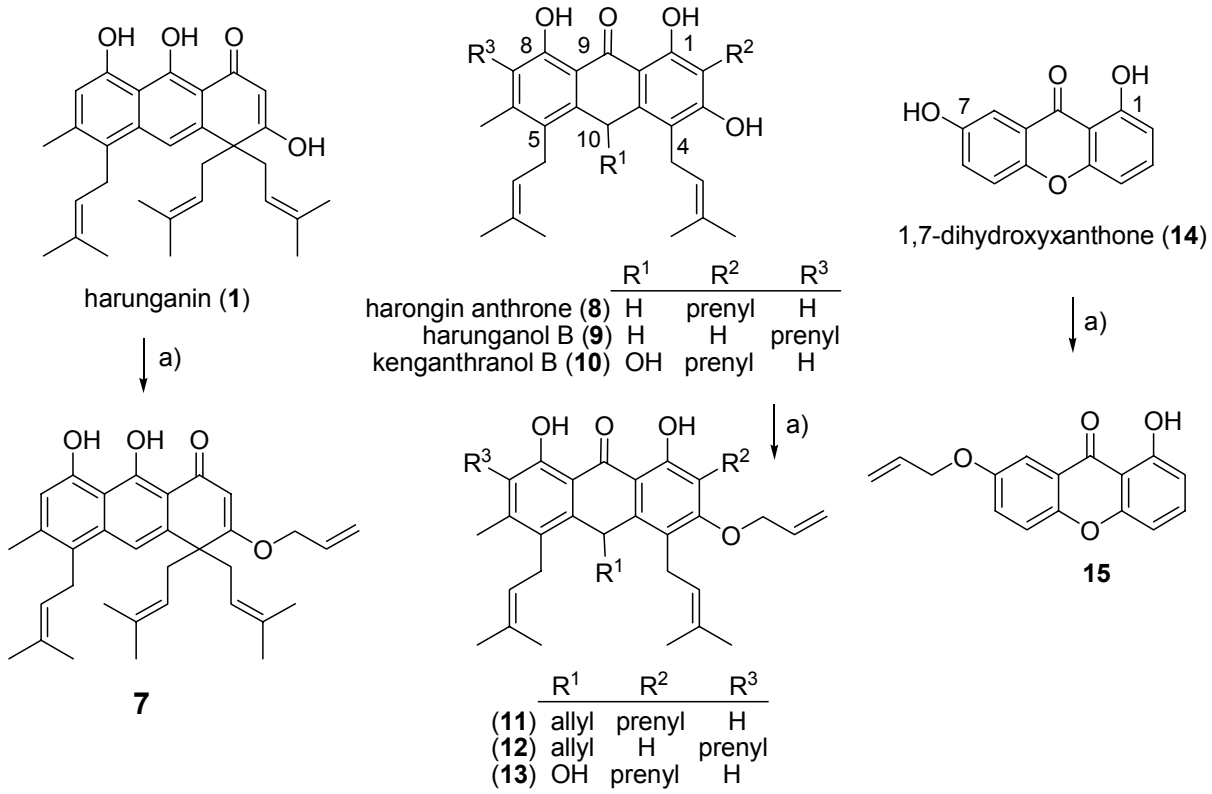
	R^1	R^2	R^3	R^4
2	H	H	H	prenyl
3	prenyl	H	H	prenyl
4	H	H	prenyl	prenyl
5	H	prenyl	H	prenyl
6	prenyl	H	prenyl	H

Scheme 1. Rearrangement products of harunganin (**1**) in dichloromethane solution.

The anthrone HR_2 (**3**), harunganol A (**2**) and B (**4**), and harongin anthrone (**5**) were previously obtained upon the thermal rearrangement (20 min at 150 °C, then 10 min at 170 °C) of harunganin (**1**) by Monache et al.[5] One new compound, the anthrone B (**6**) was observed in

the long term boiling in dichloromethane. The structures of these compounds were elucidated by comparison of their spectroscopic data with those reported in the literature.[1-5]

O-Allylation of harunganin (**1**) gave one major *O*-allylation product **7** (Scheme 2). During this short term heating in acetone, no major prenyl migration was observed. Not surprisingly, the chelated hydroxyl groups at C-8 and C-9 were not allylated. Harongin anthrone (**8**) and harunganol B **(9**) gave bisallylation products. In addition to the *O*-allylation of the non-chelated hydroxy group at C-3, a *C*-allylation of the C-H-acidic benzylic anthrone position occurred to afford the products **11** and **12**, respectively. The mass spectra of these products showed introduction of one or two allyl units in the molecule. The presence of allyl groups was supported by the signals in the ^{1}H NMR spectra for compound **11** at δ_H 4.29 (2H, d, J = 5.3 Hz, H-1′), 6.06 (1H, ddd, J = 5.3, 10.6, 17.1 Hz, H-2′), 5.25 (1H, d, J = 10.6 Hz, H-3′a), 5.40 (1H, d, J = 17.1 Hz, H-3′b) due to the presence of *O*-allyl group and at δ_H 2.39 (2H, dd, J = 7.8, 13.7 Hz, H-1″), 5.27 (1H, ddd, J = 7.8, 9.8, 16.8 Hz, H-2″), 4.57 (1H, d, J = 9.8 Hz, H-3″a), 4.81 (1H, d, J = 16.8 Hz, H-3″b) due to the *C*-allylation. The position of these groups was also supported by HMBC experiments.



Scheme 2. Allylation of phenolic constituents of *Harungana madagascariensis*. a) K_2CO_3, acetone, 1.5 h reflux.

Interestingly, kenganthranol A (**10**) with a benzylic hydroxyl group at C-**10**, did not undergo allylation at this sterically hindered hydroxyl group and gave one major product **13** with allylation of the non-chelated phenolic hydroxyl group at C-3. As expected, 1,7-dihydroxyxanthone (**14**) gave only the mono-allylation product **15** with reaction of the non-chelated hydroxyl group at C-7.

In summary, the long term thermal decomposition in dichloromethane of harunganin (**1**) gave products also found as natural constituents in *H. madagascariensis* and similar rearrangements may occur in biosynthesis. During the allylations of some phenolic anthranoids only the more reactive non-chelated hydroxyl groups reacted. *C*-Allylation was observed in the reaction of harongin anthrone (**8**) and harunganol B (**9**) to yield the *O*- and *C*-bisallylation products **11** and **12**, respectively.

Experimental Section

General Procedure. Melting points were determined on a Büchi 535 melting point apparatus and are uncorrected. The IR spectra were obtained in $CHCl_3$ a JASCO 302-A spectrophotometer. UV spectra were recorded on a Hitachi UV 3200 spectrophotometer. ^1H and 2D NMR spectra were run on Bruker AMX 400 and AMX 500 MHz NMR spectrometers. Mass spectra were obtained with a Varian Model MAT 311 spectrometer at 70 eV. HREIMS were taken on a JEOL HX 110 mass spectrometer. Silica gel [Kieselgel 60 (0.063-0.200 mm) were used for column chromatography; precoated silica gel plates (Merck, Kieselgel 60 F254, 0.25 mm and 1 mm) were used for TLC and preparative TLC analysis. Spots were visualized under UV light (254 and 366 nm) and by spraying with ceric sulfate followed by heating.

Thermal rearrangement of harunganin (1). Harunganin **(1)** (85 mg) was refluxed in dichloromethane (30 mL) for 90 h. The crude products were purified by silica gel column chromatography. Hexane-ethyl acetate (99:1) eluted successively compounds **2** (13.2 mg), **4** (8.6 mg), **3** (17.0 mg), **5** (6.0 mg), and **6** (4.2 mg). The respective structures were assigned by comparison with literature values.[1-5]

Typical procedure for allylation of phenolic compounds 7-10 and 14. The procedure used was similar for all allylations. A solution of the compound in anhydrous acetone (10 mL) was added to a suspension of potassium carbonate (1.0 g). Allyl bromide was added drop wise and the mixture was reflux for 1.5 h. After removal of the solvent, water was then added and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with water (50 mL), dried ($MgSO_4$) and concentrated in vacuum. The residue was examined by TLC using the mixture of hexane-ethyl acetate (96:4) as eluent.

3-*O*-Allylharunganine (7). Allyl bromide (300 mg, 2.4 mmol) was added to a solution of harunganin (**1**) (15 mg, 0.033 mmol) following the procedure described above. After completion of the reaction (TLC monitoring), work up was carried out and the residue was chromatographed on silica gel. The fraction containing **7** was purified on preparative TLC (PTLC) to give an

orange oil (11.5 mg, 71 %). UV λ_{max} nm $(CH_3)_2CO$) (log ε): 206 (4.25), 239 (4.37), 282 (4.08), 413 (3.77); IR ν_{max} ($CHCl_3$) cm^{-1}: 3743, 2922, 1603, 1576, 1448, 1386, 1219, 1176, 979, 772; ^1H NMR (400 MHz, $CDCl_3$): 5.72 (1H, s, H-2), 6.69 (1H, s, H-7), 9.97 (1H, s, 8-OH), 16.74 (1H, s, 9-OH), 7.34 (1H, s, H-10), 2.57 (2H, dd, *J* = 6.7 Hz, 13.8, H-11a/11'a), 2.95 (2H, dd, *J* = 6.7, 13.8 Hz, H-11b/11'b), 4.56 (1H, t, *J* = 6.7 Hz, H-12/12'), 1.44 (3H, s, CH_3-13/13'), 1.42 (3H, s, CH_3-13/13'), 2.52 (2H, d, *J* = 6.0 Hz, H-16), 5.02 (1H, t, *J* = 6.0 Hz, H-17), 1.87 (3H, s, CH_3-18), 1.65 (3H, s, CH_3-18), 2.40 (3H, s, CH_3-21), 4.45 (2H, d, *J* = 5.4 Hz, H-1′), 6.06 (1H, ddd, *J* = 5.4, 10.6, 17.3 Hz, H-2′), 5.34 (1H, dd, *J* = 1.2, 10.6 Hz, H-3′a), 5.42 (1H, dd, *J* = 1.2, 17.3 Hz, H-3′b); HRMS *m/z* 500.2920 (calc. $C_{33}H_{40}O_4$, 500.2926) ; EIMS *m/z* (%) 500 (15), 459 (4), 431 (100), 403 (10), 389 (12), 375 (32), 363 (71), 347 (15), 333 (12), 321 (24), 69 (18).

3-Allyloxy-10-allyl-1,8-dihydroxy-2,4,5-tris-(3,3-dimethylallyl)-6-methylanthrone (11). Allylation of harongin anthrone (**8**) (20 mg, 0.043 mmol) using allyl bromide (400 mg, 6.6 mol) and following the procedure described above gave a yellow oil after silica gel column chromatography and PTLC using hexane-ethylacetate (4%) as eluent (12.5 mg, 53 %), ^1H NMR (500 MHz, $CDCl_3$): 12.66 (1H, s, OH-1), 6.69 (1H, s, H-7), 12.20 (1H, s, OH-8), 4.68 (1H, t, *J* = 7.8 Hz, H-10), 3.29 (1H, dd, *J* = 6.3, 16.0 Hz, H-11a), 3.58 (1H, dd, *J* = 6.3, 16.0 Hz, H-11b), 4.90 (1H, s, H-12), 1.76 (3H, s, CH_3-14), 1.67 (3H, s, CH_3-15), 3.36 (2H, m, H-16), 5.23 (1H, s, H-17), 1.76 (s, CH_3-19), 1.67 (s, CH_3-20), 2.29 (s, H-21), 3.36 (m, H-22), 5.04 (1H, t, *J* = 6.6 Hz, H-23), 1.76 (3H, s, CH_3-25), 1.67 (3H, s, CH_3-26), 4.29 (2H, d, *J* = 5.3 Hz, H-1′), 6.06 (1H, ddd, *J* = 5.3, 10.6, 17.1 Hz, H-2′), 5.25 (1H, d, *J* = 10.6 Hz, H-3′a), 5.40 (1H, d, *J* = 17.1 Hz, H-3′b), 2.39 (2H, dd, *J* = 7.8, 13.7 Hz, H-1″), 5.27 (1H, ddd, *J* = 5.3, 9.8, 16.8 Hz, H-2″), 4.57 (1H, d, *J* = 9.8 Hz, H-3″a), 4.81 (1H, d, *J* = 16.8 Hz, H-3″b); EIMS *m/z* (%) 540 (15), 499 (100), 443 (16), 431 (50), 415 (11), 403 (13), 376 (12), 359 (16), 347 (12), 95 (26), 69 (87).

3-Allyloxy-10-allyl-1,8-dihydroxy-4,5,7-tris-(3,3-dimethylallyl)-6-methylanthrone (12). Allylation of harunganol B (**9**) (15 mg, 0.033 mmol) with allyl bromide (300 mg, 2.4 mol) using the procedure described above gave yellow crystals after silica gel column chromatography using hexane-ethylacetate (2%) as eluent (10 mg, 56%); mp 103 °C; UV λ_{max} nm (MeOH) (log ε): 204 (4.50), 283 (3.87), 379 (4.12); IR ν_{max} ($CHCl_3$) cm^{-1}: 3448, 2923, 1596, 1438, 1379, 1296, 1263, 1219, 1170, 978, 833, 772; ^1H NMR (400 MHz, $CDCl_3$): 12.64 (1H, s, OH-1), 6.32 (1H, s, H-2), 12.74 (1H, s, OH-8), 4.67 (1H, t, *J* = 7.9, H-10), 3.26 (1H, dd, *J* = 6.3, 15.3 Hz, H-11a), 3.56 (1H, dd, *J* = 6.3, 15.3 Hz, H-11b), 5.01 (1H, s, H-12), 1.75 (3H, s, H-14), 1.63 (3H, s, H-15), 3.40 (2H, d, *J* = 6.0 Hz, H-16), 4.94 (1H, t, *J* = 5.9 Hz, H-17), 1.78 (3H, s, H-19), 1.68 (3H, s, H-20), 2.26 (3H, s, H-21), 3.44 (2H, d, *J* = 6.5 Hz, H-22), 5.06 (1H, t, *J* = 6.6 Hz, H-23), 1.78 (3H, s, H-25), 1.68 (3H, s, H-26), 4.56 (2H, d, *J* = 5.0 Hz, H-1′), 6.02 (1H, ddd, *J* = 5.0, 10.6, 17.3 Hz, H-2′), 5.28 (1H, dd, *J* = 1.4, 10.6 Hz, H-3′a), 5.40 (1H, dd, *J* = 1.4, 17.3 Hz, H-3′b), 2.40 (2H, dd, *J* = 5.3, 7.9 Hz, H-1″), 5.29 (1H, ddd, *J* = 5.3, 10.0, 17.8 Hz, H-2″), 4.79 (1H, dd, *J* = 1.8, 10.0 Hz, H-3″a), 4.59 (1H, dd, *J* = 1.8, 17.8 Hz, H-3″b); EIMS *m/z* (%): 540 (9), 499 (100), 471 (16), 459 (4), 443 (15), 415 (8), 375 (31), 69 (7).

3-Allyloxy-1,8,10-trihydroxy-2,4,5-tris-(3,3-dimethylallyl)-6-methylanthranol (13). Allylation of kenganthranol B (**10**) (10.5 mg, 0.022 mmol) was performed with allyl bromide

(300 mg, 2.4 mol) using the procedure described above gave a yellow oil after silica gel column chromatography using hexane-ethylacetate (2%) as eluent (4.5 mg, 39 %), ^{1}H NMR (500 MHz, $CDCl_3$): 12.75 (1H, s, OH-1), 6.81 (1H, s, H-7), 12.26 (1H, s, OH-8), 5.98 (1H, d, *J* = 5.5 Hz, H-10), 2.15 (1H, d, *J* = 5.5 Hz, OH-10), 3.39 (1H, dd, *J* = 5.9, 15.0 Hz, H-11a), 3.50 (dd, *J* = 5.9, 15.0 Hz, H-11b), 4.99 (2H, t, *J* = 5.9 Hz, H-12), 1.80 (3H, s, H-14), 1.68 (3H, s, H-15), 3.63 (2H, d, *J* = 6.1 Hz, H-16), 5.13 (1H, t, *J* = 6.1 Hz, H-17), 1.75 (3H, s, H-19), 1.68 (3H, s, H-20), 2.32 (3H, s, H-21), 3.40 (2H, d, *J* = 6.0 Hz, H-22), 5.22 (1H, t, *J* = 6.0 , H-23), 1.80 (3H, s, H-25), 1.68 (3H, s, H-26), 4.33 (2H, d, *J* = 5.0 Hz, H-1′), 6.06 (1H, ddd, *J* = 5.0, 10.6, 16.9 Hz, H-2′), 5.26 (1H, d, *J* = 10.6 Hz, H-3′a), 5.42 (1H, d, *J* = 16.9 Hz, H-3′b); EIMS *m/z* (%.) 516 (4), 498 (27), 460 (51), 444 (43), 429 (27), 419 (12), 403 (26), 391 (13), 385 (64), 375 (23), 361 (26), 335 (13), 321 (15), 279 (18), 167 (42), 149 (100), 83 (81), 78 (30), 71 (28), 62 (30), 57 (39).

1-Hydroxy-7-allyloxyxanthone (15). To an acetone solution of 1,7-hydroxyxanthone (**14**) (3.7 mg, 0.016 mmol) was added allyl bromide (100 mg, 0.83 mmol) and potassium carbonate (1.0 g, 7.2 mmol) and the mixture was treated using the main procedure described above. A solid crystallized from hexane-ethyl acetate mixture (47/3) and the filtration gave yellow crystals (3.8 mg, 87%), mp 101 °C; UV λ_{max} nm (MeOH) (log ε): 201 (4.01), 235 (3.90), 259 (4.00), 287 (3.86), 386 (3.52); ^{1}H NMR (300 MHz, $CDCl_3$): 12.65 (1H, s, OH-1), 6.78 (1H, d, *J* = 8.2 Hz, H-2), 7.57 (1H, t, *J* =8.2 Hz, H-3), 6.91 (1H, d, *J* = 8.2 Hz, H-4), 7.41 (1H, d, *J* = 9.0 Hz, H-5), 7.37 (1H, dd, *J* = 2.7, 9.0 Hz, H-6), 7.61 (1H, d, *J* = 2.7 Hz, H-8), 4.63 (1H, d, *J* = 5.3 Hz, H-1′), 6.07 (1H, ddd, *J* = 5.3, 10.4, 17.2 Hz, H-2′), 5.32 (1H, dd, *J* = 1.3, 10.4 Hz, H-3′a), 5.45 (1H, dd, *J* = 1.3, 17.2 Hz, H-3′b); HRMS *m/z* 269.0808 (calc. $C_{16}H_{13}O_4$, 269.0813); EIMS *m/z* (%): 268 (75), 239 (14), 227 (100), 171 (52), 115 (51), 107 (32), 89 (15), 63 (42).

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