Regioselective Ring Opening of Steroidal Epoxide with Hydrides: Formation of C(2)- and C(3)-Deoxyasiatic Acid Derivatives

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Asiaticoside **1** has been used for wound healing treatment for a long time (Lawrence *et al.*, 1967; Anne *et al.*, 1968). As part of our program toward the development of new wound healing agents, we modified asiatic acid **2**, the aglycone of **1** which can be easily prepared from **1** (Shim *et al.*, 1996). Mechanistic investigations have shown that the wound healing effect is associated with the control of the collagen biosynthesis (Bonte *et al.*, 1994). Structurally the three hydroxyl groups of asiaticoside **1** and asiatic acid **2** make less efficient in transportation into the skin due to their high polarity. So we started the structure-activity relationship study by elimination of hydroxyl groups regioselectively to enhance the topical wound healing activity.

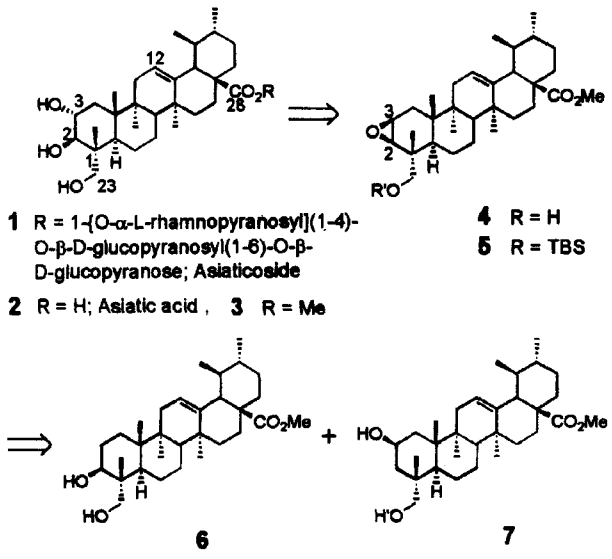

Fig. 1. Structures of asiaticoside, asiatic acid and deoxyasiatic acid methyl ester.

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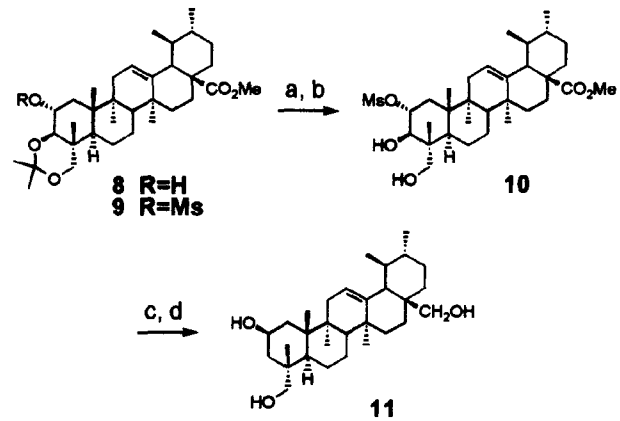
Reported herein is the highly regioselective hydride addition to methyl C(2),C(3)-epoxy-C(23)-hydroxyurs-C(12)-ene-C(28)-oate **4**, easily available from asiaticoside **1** via asiatic acid methyl ester **3**, to afford C(2)-deoxy-asiatic acid methyl ester **6** or C(3)-deoxyasiatic acid methyl ester **7** (Fig. 1).

The preparation of epoxide **4** and its reductive ring opening using lithium aluminum hydride (LAH) were reported previously and was shown in Scheme 1 (Jew *et al.*, 1998). **8** obtained from **1** (Sung *et al.*, 1992) was treated with methanesulfonyl chloride and triethylamine in methylene chloride to give methanesulfonate **9** which was converted to **10** by deprotection with *p*-toluenesulfonic acid in methanol. By using potassium carbonate in methanol, epoxidation of **10** was performed to afford the desired **4**. And then, ring opening of **4** by LAH took place in preference to axial hydride addition at C(3) to give trans-diaxial product via the chair form intermediate but the ester moiety was also reduced as we expected (Valls *et al.*, 1961; Furst *et al.*, 1949).

In order to prevent ester reduction, we used borane (BH_3) and borohydride reagents (Brown *et al.*, 1968) instead of LAH. Results are summarized in Table I.



Reagents: a) MsCl, Et_3N, CH_2Cl_2, rt, 93%; b) p-TsOH, MeOH, rt, 94%; c) K_2CO_3, MeOH, rt, 89%. d) $LiAlH_4$, THF, reflux, 100%.

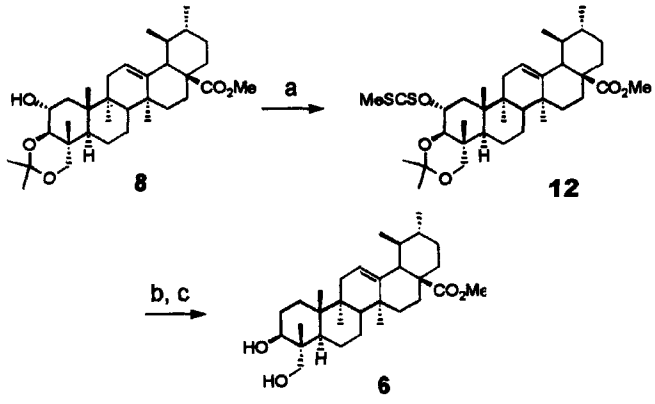
Scheme 1. Synthesis of 2β, 3β-epoxyasiatic acid methyl ester and its reductive ring opening.

Table I. The regioselective epoxide ring opening with various reagents and conditions

4 or **5** —Hydride→ **6** + **7**

Entry	Substrate	Reagents and Conditions	t (day)	Yield (%)	Ratio (6 : 7)[a]
1	**4**	$NaBH_4$, MeOH, reflux	3	0	
2	**4**	BH_3, $NaBH_4$, THF, reflux	1	83	3.0 : 1.0
3	**5**[b]	BH_3, $NaBH_4$, THF, reflux	3	41	5.5 : 1.0
4	**4**	$LiBH_4$, THF, reflux	1.5	41	1.0 : 10.5

[a]Product ratios were determined by isolated yields after silica gel column chromatography. [b]During the reaction, a partial deprotection was occurred and then the resulting crude mixture was deprotected with TBAF.



No reaction occurred with sodium borohydride ($NaBH_4$) only (entry 1), however, the reduction by BH_3 in presence of $NaBH_4$ provided a mixture of **6** and **7** (Jung *et al.*, 1998) with reverse regioselectivity as compared with the aforesaid reduction. This result may be rationalized by suggesting that the opening of the epoxide at C(2) takes place through intermolecular attack of $NaBH_4$ on a ternary complex of BH_3, C(24)-OH and oxygen of epoxide. In case of tert-butyldimethylsilyl (TBS) ether **5**, the regioselectivity was increased in comparison with **4** (entry 3). This seems to be due to the steric hindrance of TBS moiety in axial hydride attack at C(3). With lithium borohydride ($LiBH_4$) as a reducing agent, reduction of **4** afforded **7** as a major product, in which ester group remain intact (entry 4).

In conclusion, we developed highly regioselective reduction method to prepare C(2)- and C(3)-deoxyasiatic acid derivatives with conventional hydride reagents. Lithium borohydride reduced **4** to **7** highly regioselectively through axial attack at C(3), while **4** was exclusively reduced to **6** with borane in presence of sodium borohydride by attacking at C(2). The biological evaluations of these derivatives are currently being investigated.

The structure was confirmed by spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR, high resolution mass).

Compound **4**: m.p. 230~240°C; IR (KBr): 3460, 1730, 1470, 1395 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.74 (s, 3H), 0.86 (d, 3H, *J*=6.4 Hz), 0.94 (d, 3H, *J*= 5.1 Hz), 0.96 (s, 3H), 1.06 (s, 3H), 1.12 (s, 3H), 3.11 (d, 1H, *J*=4.0 Hz), 3.27 (m, 1H), 3.31 (m, 1H), 3.56 (m, 1H), 3.60 (m, 1H), 5.27 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 15.6, 16.8, 17.0, 17.3, 19.2, 21.2, 23.3, 23.6, 24.2, 27.9, 30.7, 32.3, 36.3, 36.6, 37.5, 38.1, 38.9, 39.1, 39.6, 42.2, 44.9, 47.6, 48.1, 51.5, 52.9, 54.2, 58.8, 69.8, 125.6, 138.1, 178.1. HRMS for $C_{31}H_{48}O_4$ requires 484.3554; found 484.3543.

Compound **6**: m.p. 220~222°C; IR(KBr): 3380, 1725, 1460 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.72 (s, 3H), 0.83 (d, 3H, *J*=6.5 Hz), 0.86 (s, 3H), 0.91 (d, 3H, *J*=5.0 Hz), 0.94 (s, 3H), 1.05 (s, 3H), 3.18 (d, 1H, *J*=11.5 Hz), 3.39 (d, 1H, *J*=10.3Hz), 3.58 (s, 3H), 3.59~3.61 (m, 1H), 3.69 (d, 1H, *J*=10.3 Hz), 5.22 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 16.9, 17.0, 19.0, 19.3, 20.0, 21.2, 23.4, 23.7, 24.3, 27.9, 30.7, 32.5, 36.6, 37.2, 37.6, 38.9, 39.1, 40.5, 42.3, 47.0, 47.0, 48.2, 51.5, 53.0, 67.5, 71.5, 125.7, 138.1, 178.1. HRMS for $C_{31}H_{50}O_4$ requires 486.3711; found 486.3707.

Compound **7**: m.p. 250~254°C; IR (KBr) 3400, 1720, 1460 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.77 (s, 3H), 0.86 (d, 3H, *J*=6.5 Hz), 0.94 (d, 3H, *J*=5.5 Hz), 0.98 (s, 3H), 1.08 (s, 3H), 1.24 (s, 3H), 3.18 (d, 1H, *J*=10.8 Hz), 3.42 (d, 1H, *J*=10.8Hz), 3.61 (s, 3H), 4.16~4.22 (m, 1H), 5.28 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 11.4, 15.8, 16.9, 17.0, 18.5, 21.2, 23.3, 23.6, 24.2, 26.8, 28.0, 30.6, 32.7, 36.6, 36.8, 38.3, 38.9, 39.0, 39.5, 41.8, 42.0, 47.5, 48.1, 49.8, 51.4, 52.9, 72.3, 125.5, 138.1, 178.1. HRMS for $C_{31}H_{50}O_4$ requires 486.3711; found 486.3703.

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Jung, Y. and Jew, S.-s. Unpublished result. Compound **6** was also obtained from **8** by different synthetic route as below. Reagents: a) NaH, CS_2, THF, reflux, then mel, reflux; b) Bu_3SnH, AIBN, benzene, reflux; c) p-TsOH, MeOH, rt.

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