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Synthesis and absolute stereochemistry of the acyl moiety of quillajasaponins

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Abstract

The acyl moiety of the quillajasaponins, one of the most important immunological adjuvants, was determined to be 3-(*S*), 5-(*S*)-dihydroxy-6-(*S*)-methyl-octanoic acid by enantioselective synthesis.

Quillajasaponins, the saponins from the *Quillaja saponaria* Molina (Rosaceae), have historically been used as commercial saponins, as well as foaming agents, in beverages, confectioneries, baked goods, dairy desserts, cosmetics, etc. Recently, tremendous attention has been given to the quillajasaponins due to the discovery that they are potent immunological adjuvants and are unique constituents in immuno-stimulating complexes (ISCOM);[1] ISCOM provides an effective means of presenting antigens to the immune system and are being used to prepare vaccines for influenza, hepatitis B, and AIDS.[1a] However, the number of quillajasaponins most likely exceeds 100.[2] One of the essential structural features of the quillajasaponins is attachment of an acyl moiety which is also important to the adjuvant activities of the quillajasaponins.[2] A C_9 acid was obtained after mild alkaline hydrolysis of quillajasaponins and it was readily converted into a δ lactone upon silica gel column chromatography. The chemical structure of the resulting lactone has been determined to be compound **1** (Fig. 1) by spectroscopic methods,[3] however, its stereochemistry has not been established.

The ^{1}H NMR signals ascribable to 2-, 3-, 4-, and 5-H having large *J* values (8–12 Hz) were observed,[3] that indicated the existence of the *trans* diaxial relationships between 2-H and 3-H, 3-H and 4-H, and 4-H and 5-H, respectively. Therefore, the relative stereochemistries at C-3 and C-5 of **1** were suggested to be as shown in Fig. 1. The absolute configurations of C-3 and C-5 were determined by application of the modified Mosher method.[4] The (+)-MTPA and (−)-MTPA esters of **1** (**2**$_R$ and **2**$_S$, respectively) were prepared. The positive and negative $\Delta\delta$ values were found on the right and left sides of the MTPA

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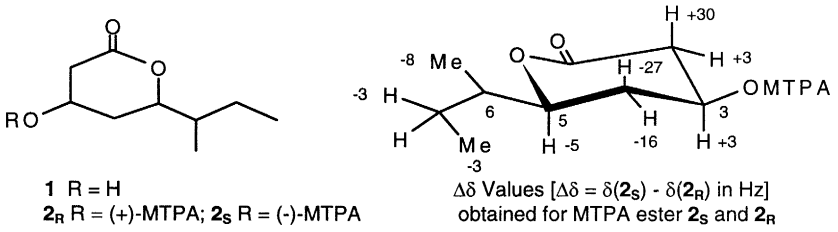
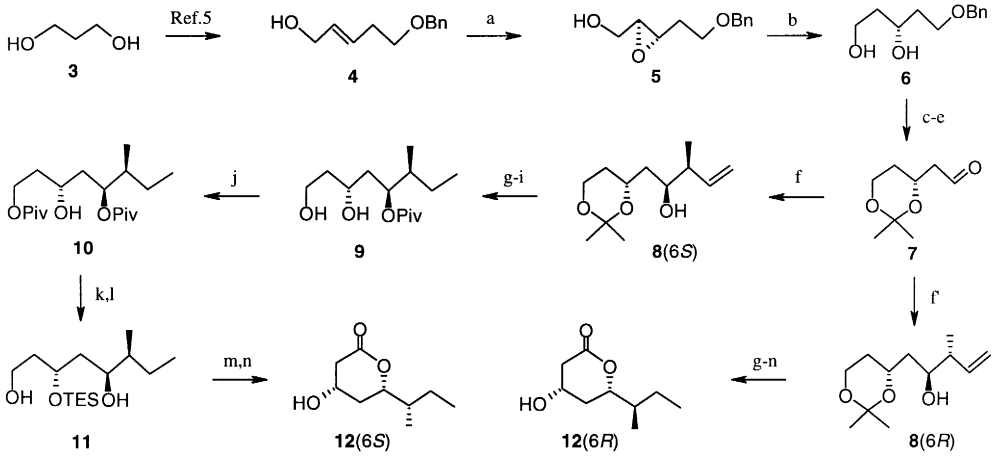


Fig. 1.

planes, respectively, indicating *S* configuration for C-3. Accordingly, the absolute configuration of C-5 was determined as *S* (Fig. 1). The stereochemistry at C-6 could not be established by spectroscopic methods, and therefore two diastereoisomers, **12**(6*R*) and **12**(6*S*), were synthesized enantioselectively and compared to the natural compound (Scheme 1).



Scheme 1. Reagents and conditions: (a) L-(+)-DET, $Ti(O^iPr)_4$, TBHP, 4 Å MS, CH_2Cl_2, −20°C, overnight; (b) Red-Al, THF, −20°C, 3 h, 91%; (c) $Me_2C(OMe)_2$, *p*-TsOH, 100%; (d) H_2, Pd/C, EtOH, rt, 4 h, 99%; (e) Swern [O], 98%; (f) (*R*,*R*)-diisopropyltartrate-(*Z*)-(−)-crotylboronate, 4 Å MS, toluene, 73%; (f) (*R*,*R*)-diisopropyltartrate-(*E*)-(−)-crotylboronate, 4 Å MS, toluene, 69%; (g) PivCl, Py; (h) H_2, Pd/C, EtOH, rt, 5 h; (i) AcOH:H_2O (4:1), 73% (3 steps); (j) PivCl, Py, CH_2Cl_2, 95%; (k) TESOTf, Et_3N, CH_2Cl_2, 0°C; (l) DIBAL-H, CH_2Cl_2, −78°C, 82% (2 steps); (m) NMO, $RuCl_2(PPh_3)_3$, acetone, 74%; (n) TBAF, THF, 88%

The allylic alcohol **4**, prepared from 1,3-propanediol,[5] was converted into (2*R*,3*S*)-epoxide **5** under Sharpless conditions in >94% ee and 93% yield.[6] Regioselective opening of the epoxide **5** with Red-Al provided the 3,5-diol **6** in 91% yield,[7] which was then readily converted into aldehyde **7** in three steps in 98% overall yields, i.e. protection of the diol with an isopropylidene group; removal of the 1-*O*-benzyl protection; and Swern oxidation. Asymmetric crotylation of aldehyde **7** with (*R*,*R*)-diisopropyltartrate-(*Z*)-(−)-crotylboronate (Roush conditions)[8] provided the (5*S*,6*S*)-homoallylic alcohol **8**(6*S*) in good yield (73%).[9] Alternatively, crotylation of **7** with (*R*,*R*)-diisopropyltartrate-(*E*)-(−)-crotylboronate gave the corresponding (5*S*,6*R*)-homoallylic alcohol **8**(6*R*) in 69% yield.[9] Protection of the 5-OH of **8**(6*S*) with a pivaloyl group followed by hydrogenation of the double bond and removal of the isopropylidene protection produced the 1,3-diol **9** in 73% yields. Diol **9** was then subjected to PivCl and TESOTf, respectively, followed by removal of the two pivaloyl groups with DIBAL-H, to provide 1,5-diol **11** in high yields. Regioselective oxidation of diol **11** in the presence of NMO and $RuCl_2(PPh_3)_3$,[10,11] after desilylation, furnished the desired lactones **12**(6*S*) in satisfactory yields. The same procedure was then readily applied to convert **8**(6*R*) into **12**(6*R*).

The optical rotation of the synthetic lactone **12**(6*S*) ($[\alpha]_D^{20}$ +38.2, *c* 1.07, MeOH) is closer to that of the natural sample ($[\alpha]_D^{20}$ +39.5, *c* 1.15, MeOH) than the corresponding value of the synthetic **12**(6*R*) ($[\alpha]_D^{20}$ +34.7, *c* 1.32, MeOH), however this evidence is not conclusive. Fortunately, differences between the ^{1}H NMR spectra of **12**(6*S*) and **12**(6*R*) are clearly observable, with the former being completely overlapped with that of the authentic sample.[12,13] These results were further confirmed by taking NMR spectra of mixed samples of **12**(6*S*) and **12**(6*R*) with the natural sample, respectively. Therefore, the natural lactone was unambiguously assigned to be **12**(6*S*).[14] Accordingly, the C_9 acyl moiety existing in the quillajasaponins is determined to be the 3-(*S*), 5-(*S*)-dihydroxy-6-(*S*)-methyl-octanoic acid.

Acknowledgements

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References

1. (a) Morein, B. *Nature* **1988**, *332*, 287. (b) Rouhi, A. M. *C&EN* **1995**, September 11, 28. (c) Livingston, P. O.; Ragupathi, G. *Cancer Immunol. Immunother.* **1997**, *45*, 10. (d) Sjölander, A.; Cox, J. C. *Advanced Drug Delivery Review* **1998**, *34*, 321.
2. (a) Kensil, C. R.; Soltysik, S.; Wheeler, D. A.; Wu, J. Y. In *Saponins Used in Traditional and Modern Medicine*; Waller, G. R.; Yamasaki, K., Eds.; Plenum Press: New York and London, 1995; p.165. (b) van Settern, D. C.; van de Werken, G. In *Saponins Used in Traditional and Modern Medicine*; Waller, G. R.; Yamasaki, K., Eds.; Plenum Press: New York and London, 1995; p.185.
3. Higuchi, R.; Komori, T. *Phytochemistry* **1987**, *26*, 2357.
4. Kusumi, T.; Ohtani, I.; Inouye, Y.; Kakisawa, H. *Tetrahedron Lett.* **1988**, *29*, 4731.
5. Oka, T.; Murai, A. *Tetrahedron* **1998**, *54*, 1.
6. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
7. Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378.
8. (a) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339. (b) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.
9. Here we assumed that the stereochemistries at C-5 and C-6 of the resulting homoallylic alcohol (**8**) were controlled by Roush reagents based on mechanistic grounds,[8] regardless of the β-chirality occurring in the aldehyde substrate (**7**).
10. Sharpless, K. B.; Akashi, K.; Oshima, K. *Tetrahedron Lett.* **1976**, *29*, 2503.
11. Oxidation of 6-methyl-1,3,5-octanetriol, prepared from **8**(6*S*), in the presence of NMO and $RuCl_2(PPh_3)_3$,[10] did not lead to the desired δ lactone **12**(6*S*).
12. Compound **12**(6*S*): $[\alpha]_D^{20}$ +38.2 (*c* 1.07, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): 4.22 (1H, m, H-3), 4.11 (1H, ddd, *J*=12.1, 3.0, 4.1 Hz, H-5), 2.90 (1H, ddd, *J*=17.0, 5.9, 1.2 Hz, H-2_{eq}), 2.42 (1H, dd, *J*=17.0, 8.1 Hz, H-2_{ax}), 2.15 (1H, m, H-4_{eq}), 1.50–1.72 (3H, m, H-6, H-4_{ax}, H-7), 1.26 (1H, m, H-7′), 0.95 (3H, d, *J*=6.9 Hz), 0.92 (3H, t, *J*=7.4 Hz); ^{13}C NMR ($CDCl_3$): 170.87, 80.33, 64.15, 39.66, 38.78, 34.88, 24.85, 13.86, 11.52; HRMS (m/z): calcd for $C_9H_{16}O_3$: 172.1100, found: 172.1102. Compound **12**(6*R*): $[\alpha]_D^{20}$ +34.7 (*c* 1.32, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): 4.25 (1H, m, H-3), 4.10 (1H, ddd, *J*=12.0, 5.7, 2.9 Hz, H-5), 2.92 (1H, ddd, *J*=17.1, 5.9, 1.4 Hz, H-2_{eq}), 2.45 (1H, dd, *J*=17.1, 8.2 Hz, H-2_{ax}), 2.19 (1H, m, H-4_{eq}), 1.78 (1H, m, H-7), 1.52–1.68 (2H, m, H-6, H-4_{ax}), 1.26 (1H, m, H-7′), 0.93 (6H, m); ^{13}C NMR ($CDCl_3$): 171.60, 80.95, 64.87, 39.62, 38.74, 33.90, 24.74, 14.01, 11.41; HRMS (m/z): calcd for $C_9H_{16}O_3$: 172.1100, found: 172.1120.
13. In the ^{1}H NMR spectra of **12**(6*S*) and **12**(6*R*), the differences between the signals for the protons adjacent to the stereogenic center C-6 are observable: (i) the signal for H-5 of **12**(6*S*) shows ddd peak with *J*=3.0, 4.1, 12.1 Hz, while that for **12**(6*R*) shows ddd peak with *J*=2.9, 5.7, 12.0 Hz; (ii) the signal for one of the H-7 of **12**(6*S*) appears at 1.57 ppm, while that for **12**(6*R*) moves downfield to 1.78 ppm.
14. The stereochemistry at C-5 (*S*) of **12**, generated by Roush crotylation, was consistent with that established by the spectroscopic methods. This result confirmed the previous assumed stereochemistry produced by Roush crotylation.[8,9]