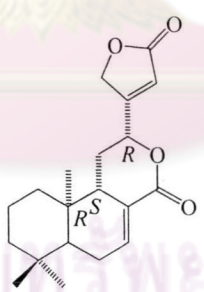
Chapter 4

Conclusions

4.1 Synthesis of (+)-Limonidilactone (33)

The (+)-Limonidilacntone (**33**) was synthesized in 6 steps from *ent*-labda-7,12(*E*),14-triene-17-oic acid (**14**). Compound **14** was cyclized to tricyclic lactone **53** with acid catalyst and then was oxidized to methyl ketone **72** by oxidizing agent. The methyl ketone **72** was converted to α-acetoxy ketone and followed by Witting reaction to **74**, and cyclized to (+)-limonidilactone (**33**) by acid catalyst in 22% over all yield.

The relative stereochemistry of (+)-limonidilactone (**33**) was confirmed by X-ray analysis. It showed optical rotation as + 14.0 ($[\alpha]_D^{20}$, *c* 0.193, $CHCl_3$). The configuration of (+)-limonidilactione (**33**) was assigned as C9(*S*), C10(*R*) and C12(*R*) as shown in below. figure.



(+)-Limonidilactone (**33**)

4.2 The Cytotoxic Activity of Modified Labdanes

The modified labdanes showed moderate cytotoxicity against human cancer cell lines, BT474 (human breast carcinoma ATCC No. HTB 20), Chago (human undifferentiated lung carcinoma), Hep-G2 (human liver hepatoblastoma ATCC No. HB 8065), Kato3 (human gastric carcinoma ATCC No. HTB 103) and SW620 (human colon adenocarcinoma ATCC No. CCL 227). The compound **54** showed strong activity against gastric carcinoma (IC_{50} 0.6 μg/ml) and breast ductal carcinoma (IC_{50} 2.5 μg/ml). Compound **54** was more selective than other labdane compounds.

The structures of the labdane diterpenes tested here, may have a strong and moderate correlation with their cytotoxic activites. However, because of the limited data concerning structure and activity of the labdane diterpenes, it is difficult to establish a clear structure-activity relationship. Compound **54**, the most cytotoxic diterpene among compounds tested, showed interesting activity. However, because it is unique among the diterpenes with cytotoxicity, it could be untimely to generalize or establish a relationship of structure.

4.3 The Effect of Inhibition with Na^+, K^+-ATPase.

From the results of Na^+, K^+-ATPase activity from rat brain, compounds **13** and **14** showed strong inhibitory activity. Compounds **47-53** showed moderate inhibitory activity and compounds **55** and **56** showed no inhibitory activity on crude enzyme Na^+, K^+-ATPase.