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Synthesis and anion recognition of a novel oleanolic acid-based cyclic dimer

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ABSTRACT

A novel cyclic dimer based on oleanolic acid was synthesized using click chemistry and it showed remarkable selectivity and affinity to bind fluoride ion through C–H···F hydrogen bond interactions which involved the delocalization of proton in methylene.

Oleanolic acid (**1**), which is a facile pentacyclic triterpenoid from medicinal plants, has been noted for the therapeutic effect on human liver disorders and antitumor-promotion effect.[1–4] Although many reports based on steroidal units have appeared in anion recognition,[5–13] there is no report about triterpenoid scaffolds which are the biogenic homologs with steroids, possessing the chiral rigid skeleton, relative low-toxicity, and biocompatibility.

In recent years, the development of receptors for recognizing anionic species has become a major area of supramolecular chemistry because of their ability to serve as models for the biological processes and their potential applications for the design of sensors in medicine and analysis.[9,14–19] Most anion binding receptors generally utilize amide, urea, pyrrole, and guanidinium groups as binding sites to form N–H···X^- hydrogen bonds.[20–31] Recently, the C–H···X^- type of interaction using the proton of methylene attracts more and more attention.[32–34]

In our previous work, the oleanolic acid derivatives with good organic gel ability, the glycyrrhetinic acid-based receptor for Hg^{2+} ion, and the stable cyclic dimer assembled by glycyrrhetinic acid conjugate were reported.[35–37] As continuation of previous work, the synthesis of a novel cyclic dimer based on oleanolic acid and its ability to recognize anions were reported here for the first time. In this cyclic dimeric molecule, the oleanolic acid moiety offered the rigid chiral skeleton to build the cavity, and the aliphatic chain containing methylene and 1,2,3-triazole groups provided the binding sites and facilitated the molecular rotation, respectively.

The synthesis of cyclic dimer based on oleanolic acid (**5**) is shown in Scheme 1. Oleanolic acid (**1**) reacted with propargyl bromide in DMF at rt to give **2**, and then coupled with bromoacetyl bromide to afford **3** in high yield. Compound **3** was treated with sodium azide in DMF at 70 °C to give **4**. Finally, compound **5** was obtained through 'click chemistry'[38] in 24% yield after column chromatographic purification. The crystal of compound **4** (Fig. 1) was obtained in the mixed solvents of methanol and tetrahydrofuran (1:4, v/v), and the X-ray crystallography showed that the alkyne and azide groups of **4** were arranged alternately and the distance between alkyne and azide was very close (see Supplementary data), which is conducive to the cycloaddition of terminal alkyne and azide.

The NMR titration was used to investigate the interaction between cyclic dimer (**5**) and the anions of $^nBu_4N^+X^-$ (X = F, Cl, Br, I, AcO). Since the methylene group played important roles in the anion recognition and chemical environments of CH_2^a and CH_2^b (Scheme 1) were very similar with each other in **5**, it was necessary to confirm the ^{1}H NMR signals of CH_2^a and CH_2^b. The HMBC spectra of 2D NMR ($CDCl_3$, 600 MHz) between the methylene protons adjoining carbonyl group and that linked to ester group (Fig. 2) showed that the signals of CH_2^b were assigned to δ 5.04, 5.07, 5.20, 5.22 ppm and CH_2^a were δ 4.98, 5.00, 5.21, 5.23 ppm, respectively.

The results of NMR titration showed that significant changes were observed only for F^- ion in its ^{1}H NMR spectra, while there was no shift for the other ions (Br^-, Cl^-, I^- and AcO^-) (see Supplementary data). The remarkable selectivity should attribute to the size of cyclic dimer cavity and the fluoride ion. However, with the increasing concentrations of $^nBu_4N^+F^-$ (TBAF), the signals of CH_2^b became weaker and weaker with nearly no shift and finally disappeared in ^{1}H NMR spectra which was different from the traditional receptors,[13,32–34] while the shifts and peaks of CH_2^a had

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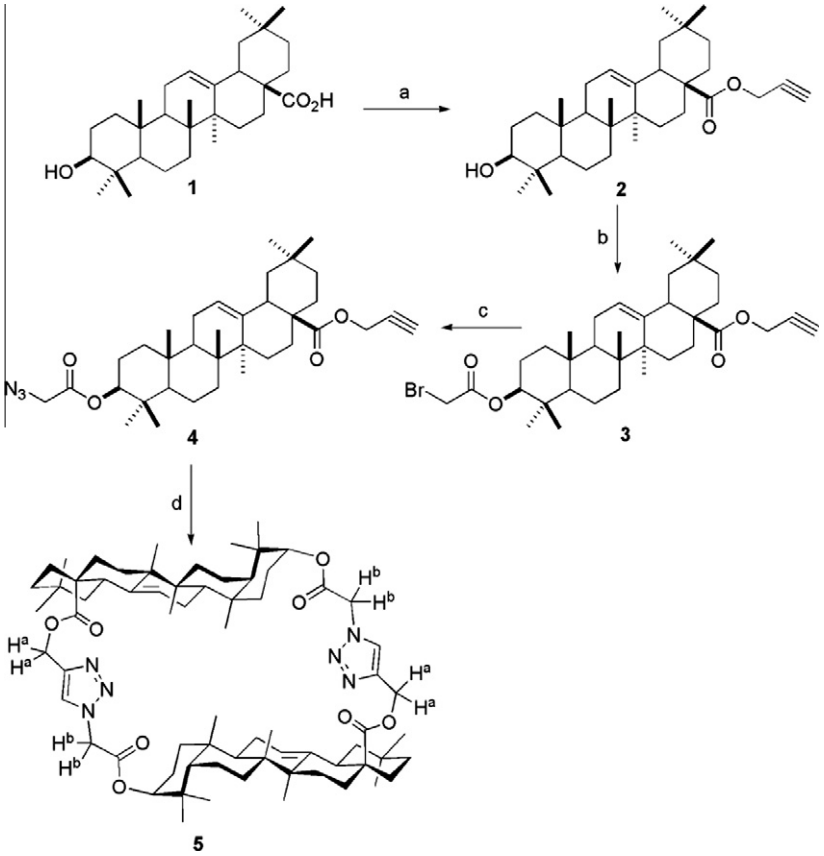

Scheme 1. Reagents and conditions: (a) $BrCH_2C{\equiv}CH$, Cs_2CO_3, DMF, rt, 92%; (b) $BrCOCH_2Br$, K_2CO_3, dry $CHCl_3$, rt, 86%; (c) NaN_3, DMF, 70 °C, 70%; (d) $CuSO_4{\cdot}5H_2O$, sodium ascorbate, *t*-BuOH, CH_3OH, H_2O, THF, 60 °C, 6 h, 24%.

no changes (Fig. 3). When the molecular ratio of [**5**]: [F^-] was 1:2, the signals of H^b had almost completely disappeared, indicating the 1:2 complex formed. Because there were no changes of chemical shifts, the binding constants could not be calculated.[39] The most reasonable explanation was as following (Fig. 4): since CH_2^b associated with the carbonyl function group, its acidity was stronger than that of CH_2^a, which appended to oxygen of ester. So the proton of CH_2^b was more likely to delocalize and it was much easier to combine with fluorine ion than CH_2^a. With the increasing concentrations of TBAF, the interaction of H···F^- would become so strong enough that the signals of H^b disappeared.[40]

In order to confirm our speculation, the UV–vis spectroscopy was used to investigate the affinity of **5** toward F^- ion. When TBAF (3 equiv) was added to the solution of **5** (4.2×10^{-4} M) in CH_2Cl_2–CH_3OH (1:1, v/v), the absorption intensity increased from 1.06 to 1.83 (almost two times of the original one), while the absorbance bands at 259 nm had nearly no changes (Fig. 5). The strong hyperchromic effect was due to the new other group appearing in the similar absorption bonds with 1,2,3-triazole at 258 nm, and the new group was probably produced by the delocalization of H_b after enough F^- ions were added. This result coincided with NMR titration.

The speculation of delocalization of H_b was also confirmed by the IR spectra (Fig. 6). The C=O stretching frequency of **5** was about 1740 cm^{-1}, while there were two C=O stretching frequencies (1830 cm^{-1} and 1730 cm^{-1}) after TBAF (3 equiv) was added. It certified that the carbonyl groups whose stretching vibration bands appeared at higher wavenumbers linked with CH_2^b, while the other carbonyl group closed to CH_2^a.

Meanwhile, the linear oleanolic acid derivative **6** was also synthesized as the control (Fig. 7), and its ability to bind F^- was investigated. The results showed that there was no change in ^1H NMR spectra when F^- was added, indicating that the cavity of the cyclic dimer should be necessary in the affinity to bind fluoride ion (see Supplementary data).

Based on the above results, the assumption binding model of cyclic dimer **5** was proposed (Fig. 8). In this cyclic dimer, the triterpenoid moiety set up the suitable cavity, CH_2^b group appended at the carbonyl offered the binding sites and 1,2,3-triazole was just the linker and used for facilitating the molecular rotation during the recognition process of F^- ion in $CHCl_3$.

In conclusion, a novel cyclic dimer based on oleanolic acid was synthesized using click chemistry. It showed remarkable selectivity and affinity for F^- ion through C–H···F^- hydrogen bond interactions by the delocalization of proton in methylene, and it might give some clue for the potential applications in biomaterials and biosensors.

Acknowledgments

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Supplementary data

Supplementary data (synthesis and structure data of compounds **2**–**6** and NMR titration of **5** with Cl^-, Br^-, I^-, AcO^- and **6**

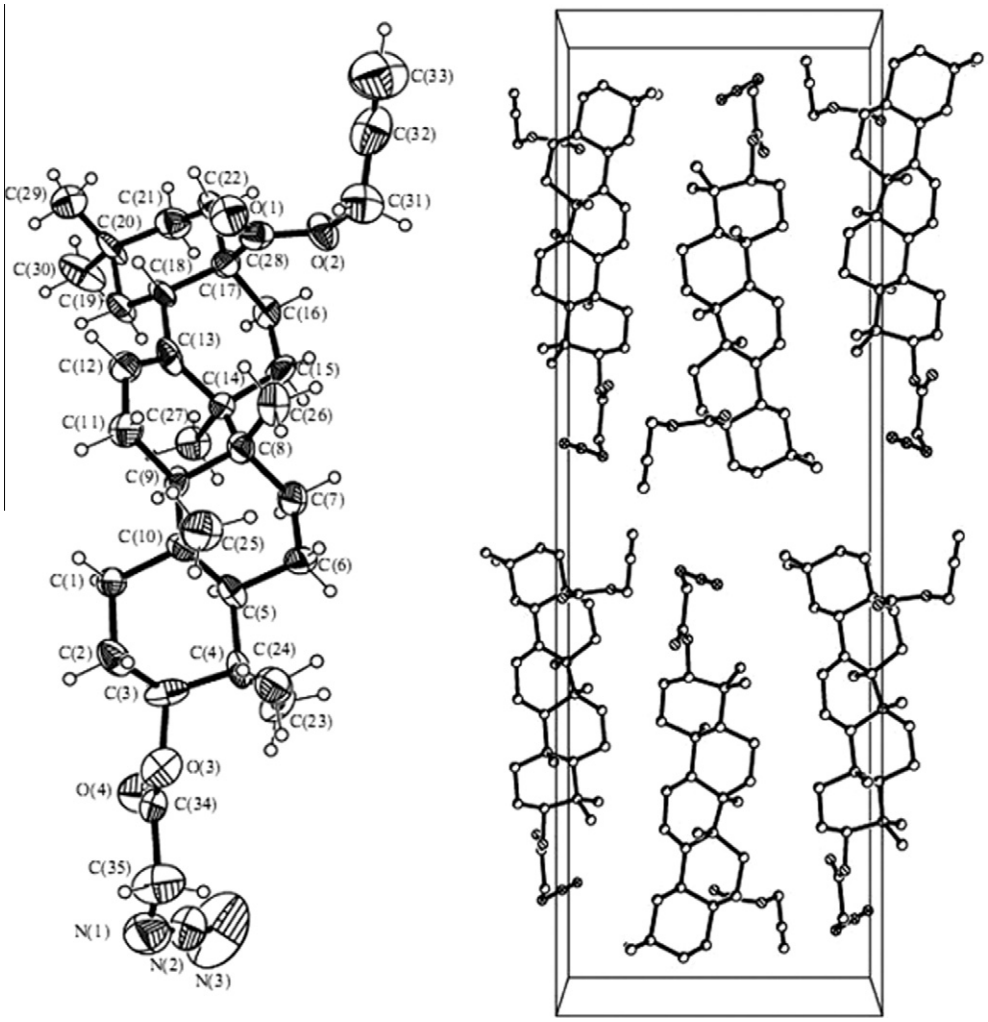

Figure 1. ORTEP drawing of **4** with 35% probability ellipsoids, showing the atomic numbering scheme (left) and a packing view along the α direction (right).

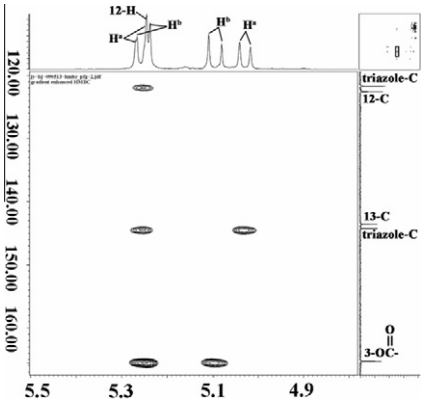

Figure 2. 2D NMR (HMBC) spectrum of cyclic dimer **5** ($CDCl_3$, 600 MHz).

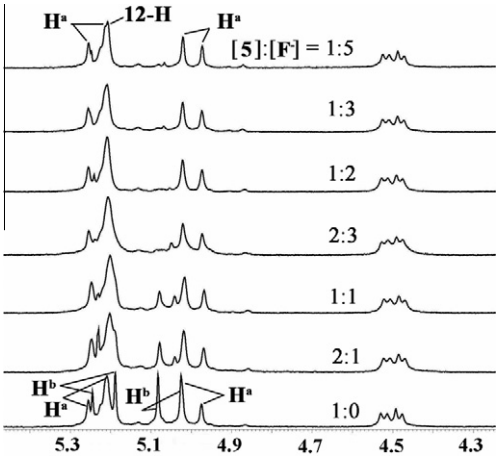

Figure 3. Unusual behavior of methylene proton with increasing F^- concentration ([**5**] = 5.0 mM, $CDCl_3$, 300 MHz); *x*-axis represents NMR chemical shift in parts per million.

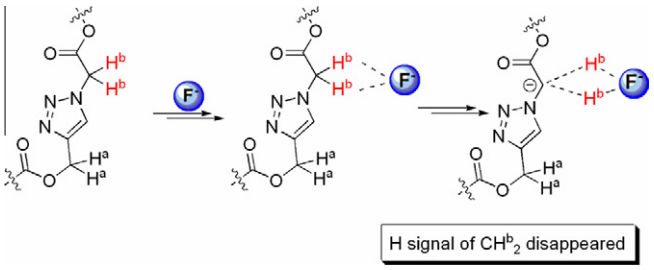

Figure 4. The possible binding process between cyclic dimer **5** and F^- ion.

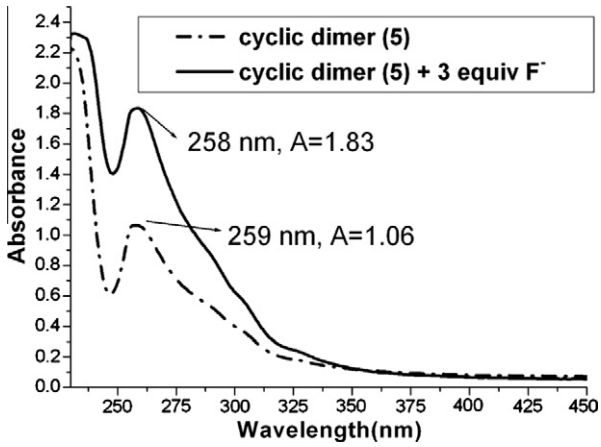

Figure 5. Absorbance spectra of cyclic dimer **5** (4.2×10^{-4} M) and cyclic dimer **5** (4.2×10^{-4} M) + 3 equiv F^- in CH_2Cl_2–CH_3OH (1:1, v/v).

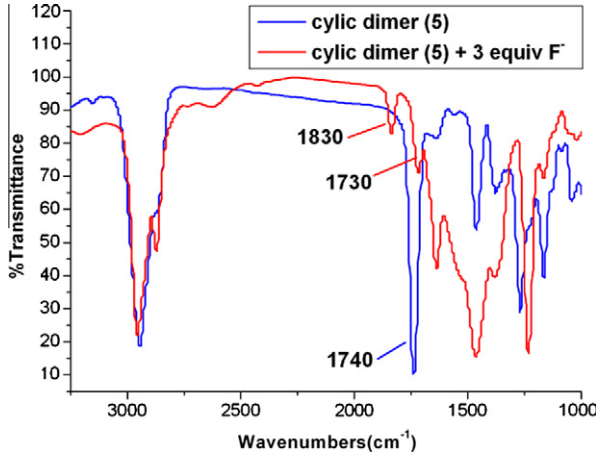

Figure 6. IR spectra of cyclic dimer **5** (blue) and **5** + 3 equiv F^- ion (red).

with F^-) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.022.

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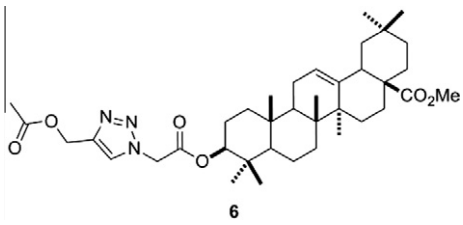

6

Figure 7. Structure of control compound **6**.

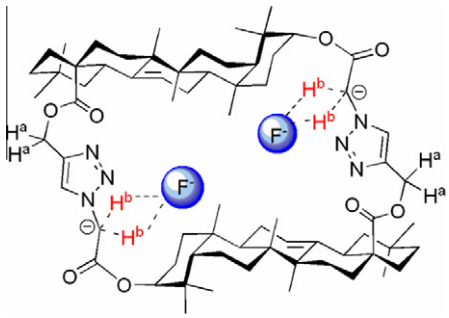

Figure 8. The assumption model of cyclic dimer **5** with F^- ion.

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