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Stereoselective synthesis of novel cyclopropyl analogues of known cysteine protease inhibitors

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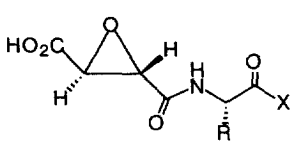
Abstract

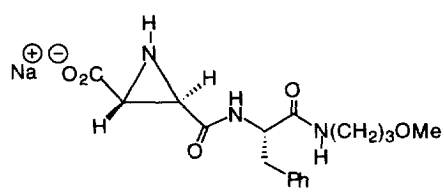
Efficient synthesis of two novel analogues of some known protease inhibitors, *via* the isosteric replacement of oxirane / aziridine moiety of the parent compounds by cyclopropane ring, is described.

Keywords : enzyme inhibitor; isostere; stereoselective; cyclopropane.

Towards developing efficient therapeutic agents to counter increased cysteine protease activity related disorders, the oxirane dicarboxylic acid derivatives **1-3** (Scheme 1) exhibited encouraging activity and were found to be selective inhibitors of papain and cysteine proteases [1]. Structure-activity relationship (SAR) studies have shown that the presence of *trans*-epoxysuccinic acid and L-leucine moieties are essential for optimum activity, whereas the terminal amide group can be modified in quest of improved activity. Interestingly, the structurally similar *trans*-aziridine dicarboxylic acid derivative **4** also displayed impressive cathepsin L inhibition activity and is a potentially useful agent for the treatment of muscular dystrophy, osteoporosis, malignant hypercalcemia etc [2]. In view of these observations, we reasoned that an isosteric replacement of the oxirane / aziridine ring of these compounds with a cyclopropyl group might be an useful approach towards attaining more active analogues and can also provide additional SAR information.

Scheme 1





1, R = Me_2CHCH_2 ; X = $N(CH_2CH_2CH_2CH_2Me_2)_2$

2, R = Me_2CHCH_2 ; X = $N(CH_2CH_2CH_2CH_2NH_2)_2$

3, R = Me_2CHCH_2, Bn, $MeSCH_2CH_2$; X = –N⟨⟩N–Ar

4

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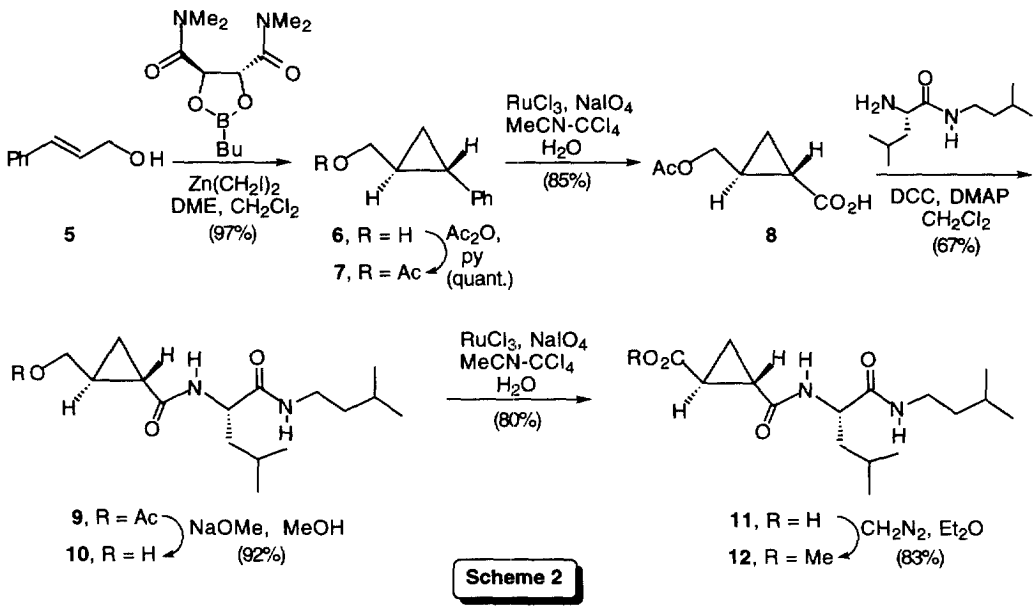
Thus, according to our recently reported protocol [3], *trans*-cinnamyl alcohol (**5**) was converted to the corresponding *trans*-cyclopropane carboxylic acid **8** (Scheme 2), *via* initial stereoselective cyclopropanation (Charetté's method) of **5** to **6** (92%ee) [4], followed by utilization of the phenyl group as a masked carboxylic acid synthon, affording enantiopure **8** in good overall yield [3]. Towards introducing the side-chain amide functionality, the acid **8** was coupled with L-leucine isoamylamide [1a] under standard reaction conditions providing the diamide derivative **9** in good yield. Finally, deacetylation of the primary alcohol to compound **10** and its oxidation to the corresponding acid resulted in the desired cyclopropane dicarboxylic acid derivative **11**, which on treatment with diazomethane under standard conditions provided the corresponding ester analogue **12**.[1]



Scheme 2

In conclusion, a short-step stereoselective route to potentially useful novel derivatives of known bioactive compounds has been developed following an efficient reaction sequence. Biological activity studies of the above compounds are currently in progress and will be reported in due course of time.

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[1] All the compounds synthesized were fully characterized by their IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.