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PREPARATIVE SYNTHESIS OF A–FLUOROCYCLOPROPYL CARBOXYLIC ACID DERIVATIVES

Cyclopropyl carboxylic acid derivatives are known to be a recurring component of various drug molecules. The above moiety usually is introduced into the molecule through different approaches, but one is exceptional: the Wadsworth-Emmons cyclopropanation [1] is a way to convert epoxides into their respective cyclopropanes selectively, yielding trans-oriented product. Such exceptional selectivity is proven to be useful on multiple occasions in introduction of cyclopropane moiety. Most recent and striking examples include total synthesis of (+)-belactosin A [2] and separate works by Merschaert [3] et al. and Singh [4] et al., where they described conversion of starting epoxides to respective cyclopropanes on a kilogram scale. This conversion is also susceptible to extensive modification of starting materials, which was shown by Bray and Minicone [5] in their acquisition of α-substituted cyclopropyl acid esters with high degree of stereocontrol (Fig. 1).

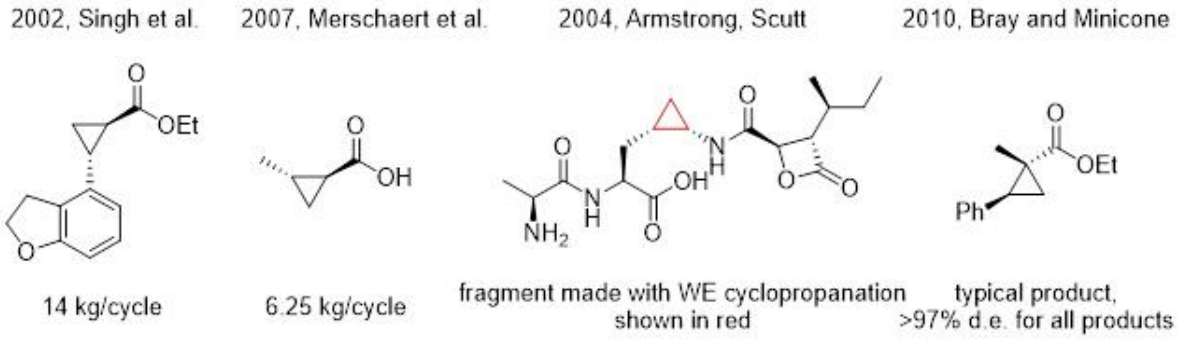

Fig. 1. Products synthesized with Wadsworth-Emmons cyclopropanation

Investigation into feasibility of the conversion started with the assay of the reaction of (R)-styrene oxide and triethyl 1-fluoro-1-phosphonoacetate **1**. Phosphonoacetate **1** was reacted with butyllithium in glyme, mixed with (R)-styrene oxide and after refluxing for several days, workup and isolation, afforded cyclopropane **2a**, which after saponification, yielded acid **3a**. **3a** was found to have (R,R)-configuration with >99% diastereomeric excess.

Subsequent scale-up afforded (R,R)-**2a** with disappointingly low yield of 13%. Further optimization has shown correlations between yield and rate of reaction and temperature, nature of counterion and concentration of reagents. The choice of solvent has also proved to be detrimental, with dioxane being superior. With these revisions, it was possible to obtain ester **2** with a 30% yield.

Following these procedures, it was also possible to obtain not only optically active cyclopropanes (R,R)-**2a** and (S,S)-**2a**, but also bicyclic cyclopropanes **2b**, **2c** and spirocyclic cyclopropane **2d** (Fig. 2).

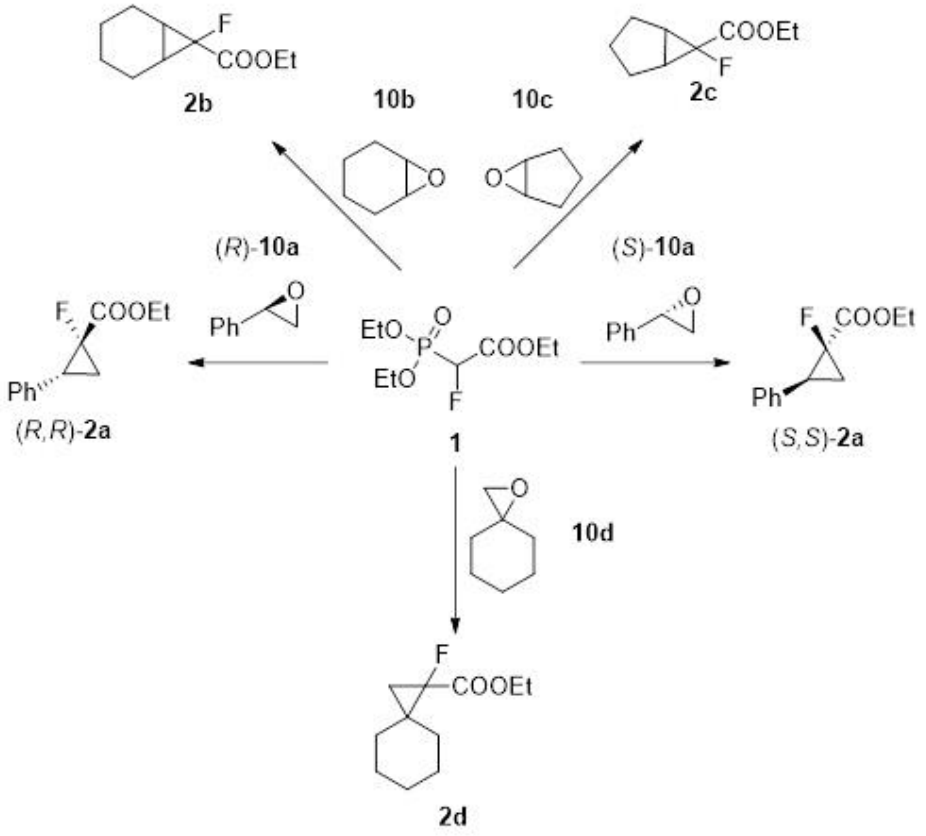

Fig. 2. Cyclopropanes made by W-E cyclopropane synthesis with phosphonoacetate 1. Conditions: BuLi, dioxane, reflux

Parallel to direct reaction of epoxides with phosphonoacetate **1**, alternative way of synthesis, based on a described pathway [6] was attempted. With intention of synthesis of cyclopropane **2**, chloroketone **4** by Friedel-Crafts acylation of benzene and subsequently reduced with sodium borohydride to yield chlorohydrin **5**.

While acquisition of lactone **7** through alkylation of phosphonoacetate **1** failed, it was found that coupling of acid **9** with chlorohydrin **5** to yield ester **6**. Ester **6** was, after some optimization, cyclicized into lactone **7**.

A compound of similar design, as described in [6], rearranged into desired cyclopropane after treatment with sodium ethanoate, generated *in situ*. A similar approach was attempted – lactone **7** was subjected to the treatment with sodium ethanoate in tetrahydrofuran, and, after a night of refluxing afforded a compound resembling oxophospholane **8** by NMR spectroscopy, which, upon additional reflux only yielded further uncontrolled decomposition (Fig. 3).

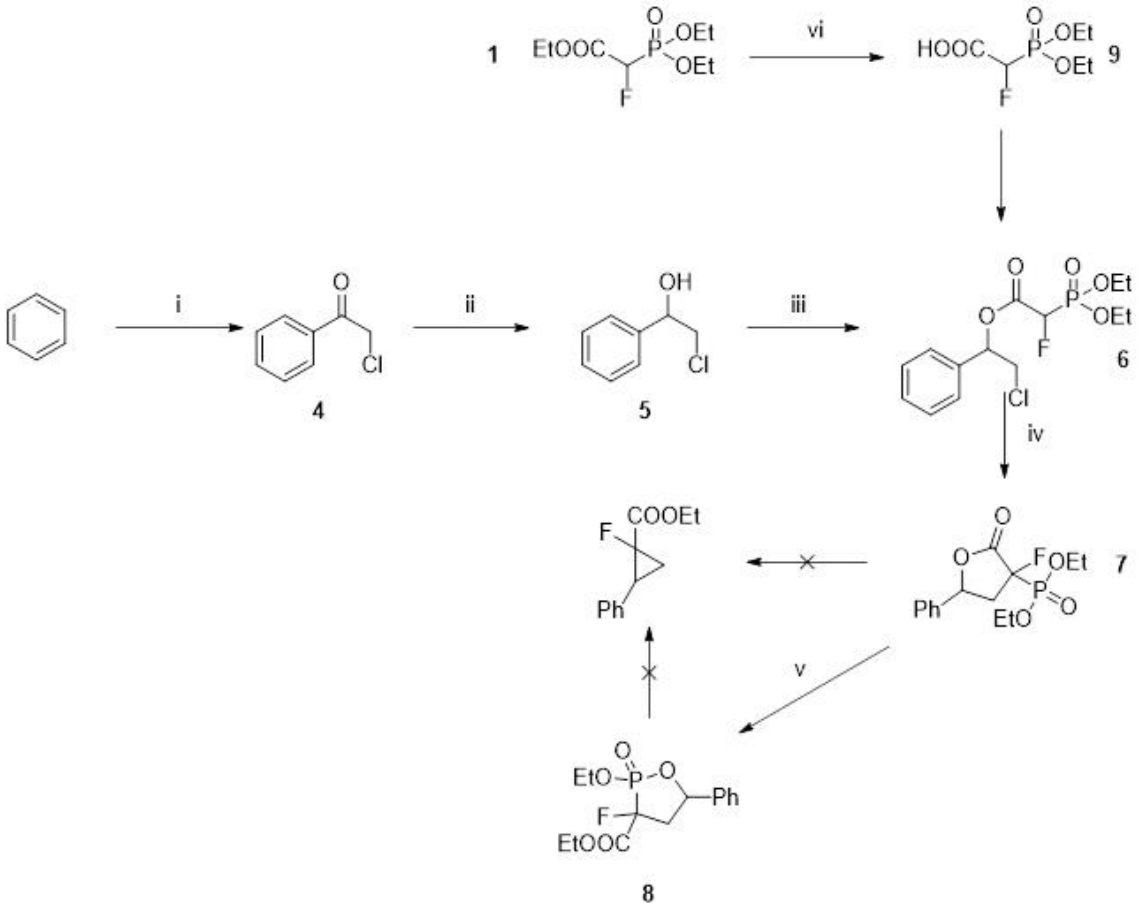

Fig. 3. Synthesis of cyclopropane 2 via alternative synthetic route. Conditions: i. $AlCl_3$, chloroacetyl chloride, CH_2Cl_2; ii. $NaBH_4$, MeOH; iii. EDC•HCl, Py, DMAP, 9; iv. NaH, THF; v. NaH, EtOH, THF, reflux

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