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Enantioselective syntheses of bicyclo[3.1.0]hexane carboxylic acid derivatives by intramolecular cyclopropanation

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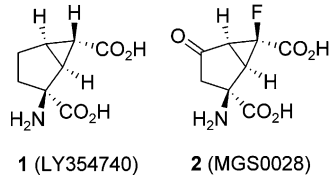
Abstract—Enantioselective syntheses of bicyclo[3.1.0]hexane carboxylic acid derivatives are described. The syntheses were achieved by an intramolecular cyclopropanation as the key step, starting from enantiomerically pure starting materials that are commercially available.

L-Glutamic acid and L-aspartic acid, referred to as excitatory amino acids, widely exist in the central nervous system (CNS) and play principal roles as neurotransmitters.[1] The glutamate receptors are generally classified into two types, ionotropic glutamate receptors (iGluR) and metabotropic glutamate receptors (mGluR). The latter class is subdivided into three groups (group I–III) on the basis of sequence homology, pharmacological features, and signal transduction mechanisms.[2–7] The group II receptors are negatively coupled to adenylate cyclase through G proteins, and the agonists of these receptors might be useful for the treatment of CNS-related disorders such as anxiety[8] and schizophrenia.[9,10]

A series of amino acids bearing a bicyclo[3.1.0]hexane core (Fig. 1), such as **1** (LY354740, Eli Lilly), are potent agonists of group II mGluR.[11,12] Recently, a 6-fluorinated derivative (**2**, MGS0028, Taisho) was found to be orally active and to be one of the most selective and potent agonists.[12] These relatively small molecules are densely functionalized and possess many stereogenic centers. Because **2** is 165-fold as active as *ent*-**2**,[12] an enantioselective route would be desirable for any preparation. Thus, the synthesis of this class of compounds constitutes an interesting challenge in terms of stereochemistry as well as the construction of the complex

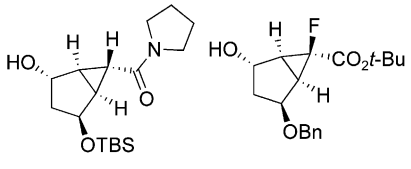


1 (LY354740) **2** (MGS0028)

Figure 1.

skeleton. While a limited number of examples have been reported,[11–16] a novel approach is awaited to realize an efficient synthesis.

We report herein our strategies for the enantioselective syntheses of 2,4-dioxybicyclo[3.1.0]hexane-6-carboxylic acid derivatives **3** and **4**, which are expected to be useful intermediates for the synthesis of **1** and **2**.[17] The syntheses were achieved by an intramolecular cyclopropanation as the key step, using starting materials that are commercially available in enantiomerically pure form.



3 **4**

Scheme 1 summarizes the synthesis of **3**. Enantiomerically pure lactone **5**, either enantiomer of which is commercially available, was treated with refluxing

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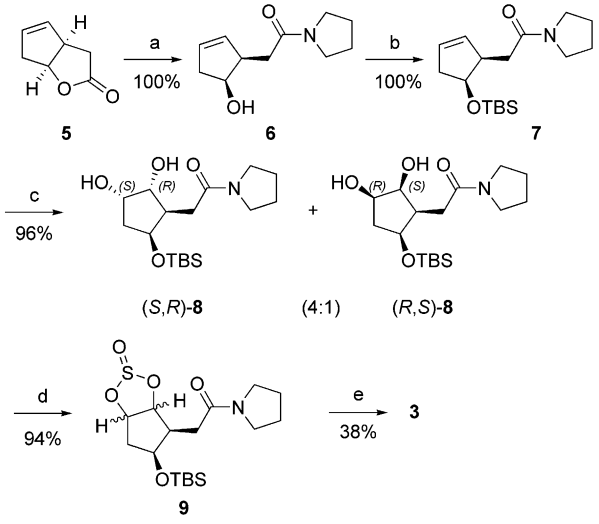
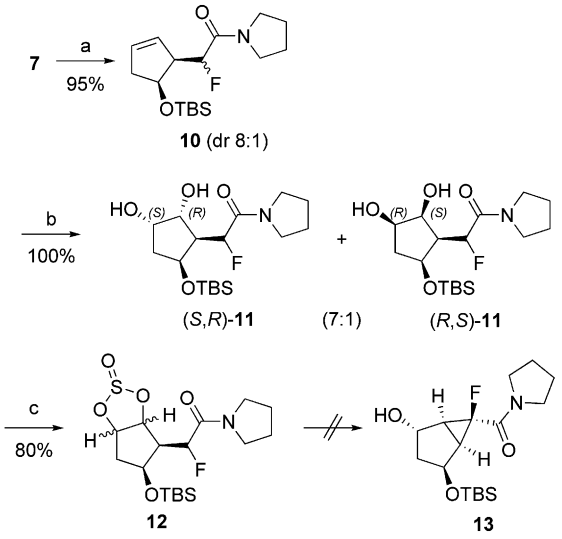


Scheme 1. Reagents and conditions: (a) pyrrolidine, reflux; (b) TBSCl, imidazole, DMF, rt; (c) NMO, OsO_4 (cat), acetone–H_2O, rt; (d) $SOCl_2$, Et_3N, toluene, 0 °C; (e) LHMDS, THF, −78 °C.



Scheme 2. Reagents and conditions: (a) $(PhSO_2)_2NF$, LDA, THF, −78 °C; then chromatographic separation of diastereomers; (b) NMO, OsO_4 (cat), acetone–H_2O, rt; (c) $SOCl_2$, Et_3N, toluene, 0 °C.

pyrrolidine to give amide **6** in quantitative yield. The hydroxyl group of amide **6** was protected as a TBS ether in quantitative yield, and the resulting **7** was oxidized to diol **8** in 96% yield by an osmium-catalyzed dihydroxylation with 4:1 diastereoselectivity. The mixture of diastereomers **8** was treated with thionyl chloride in the presence of triethylamine to afford cyclic sulfite **9** in 94% yield. Intramolecular cyclopropanation was accomplished using LHMDS to give bicyclic alcohol **3** in 38% yield (based on the major diastereomer of **8**).

Fluorinated cyclopropanes have received a high level of interest, and the chemistry has recently been reviewed.[18] While carbene chemistry had been dominant in the synthesis of monofluorinated cyclopropanes, Taguchi reported non-carbene approaches, a tandem Michael/cyclization process in 1994,[19] and an intramolecular displacement of an iodide by a fluoro ester enolate in 2001.[20] Scheme 2 summarizes our attempts to extend the strategy described above to the synthesis of a 6-fluorinated derivative, which would lead to **2**. Fluorination of TBS-protected amide **7** using *N*-fluorobenzenesulfonimide[21] and LDA afforded **10** in 95% yield with a diastereomeric ratio of 8:1. The major diastereomer was isolated by silica gel column chromatography. Dihydroxylation of **10** gave the corresponding diol **11** in quantitative yield with a diastereomeric ratio of 7:1. Treatment of the mixture of two diastereomers with thionyl chloride in the presence of triethylamine gave cyclic sulfite **12**. The mixture of diastereomers was treated with various bases (LDA, LHMDS, KHMDS, NaHMDS, KO*t*-Bu, DBU, NaH, or LTMP) to induce intramolecular cyclopropanation; however, none of them gave the desired bicyclic compound (**13**).[22]

To gain insight into this unsuccessful cyclization, the reaction was quenched with CD_3COOD (Fig. 2). No deuterated compound **14** was formed, indicating that the deprotonation was prevented for some reason. To generate an enolate (**C**), the proton must be oriented

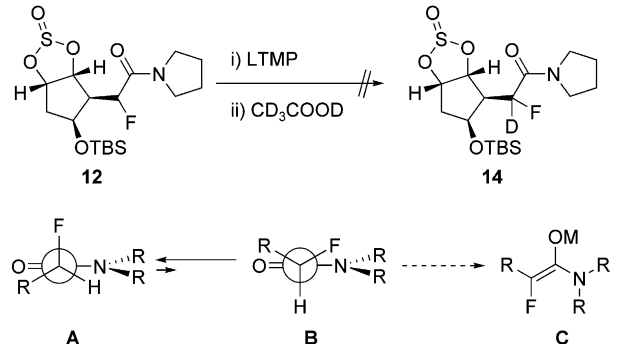
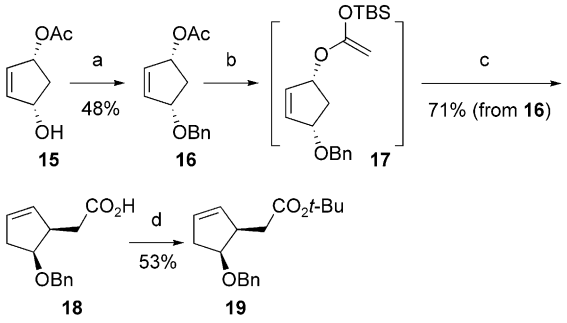


Figure 2. Deprotonation of α-fluoro pyrrolidine amide **12**.

perpendicular to the plain of the amide group, as in conformer **B**. Conformer **B** is, however, expected to be less stable than conformer **A** due to steric repulsion between the fluorine and the amide moiety. The predominance of conformer **A** over conformer **B** would prevent the deprotonation.

To facilitate the deprotonation, we tried to convert the amide to esters, which were expected to be less bulky than the amide. All attempts, however, resulted in failure because the esters re-cyclized to bicyclic lactones such as **5**. We, therefore, turned our attention to a different route to fluoroesters in order to investigate the intramolecular cyclopropanation. The synthesis of the substrate was achieved by an Ireland–Claisen rearrangement, as shown in Scheme 3. The hydroxyl group in **15** (commercially available) was protected as the benzyl ether, and resulting acetate **16** was converted to the corresponding TBS ketene acetal **17** by treatment with LDA, followed by TBSCl in the presence of HMPA.[23] The Claisen rearrangement was achieved by heating the TBS ketene acetal in xylene at 130 °C, and the resulting TBS carboxylate was hydrolyzed by aqueous NaOH



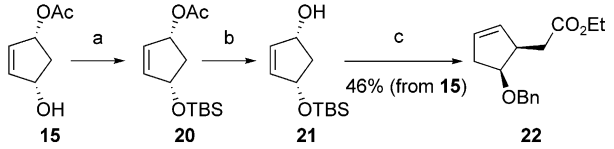
Scheme 3. Reagents and conditions: (a) BnBr, NaH, DMF, 0 °C to rt; (b) LDA, HMPA, TBSCl, THF, −78 °C to rt; (c) xylene, 130 °C; then NaOH, THF–H_2O, rt; (d) *t*-BuOH, DCC, DMAP, CH_2Cl_2, 0 °C to rt.

in THF to afford carboxylic acid **18** in 71% yield (three steps from **16**).[23] Esterification of **18** to give *tert*-butyl ester **19** was effected by treatment with *t*-BuOH and DCC in the presence of DMAP.

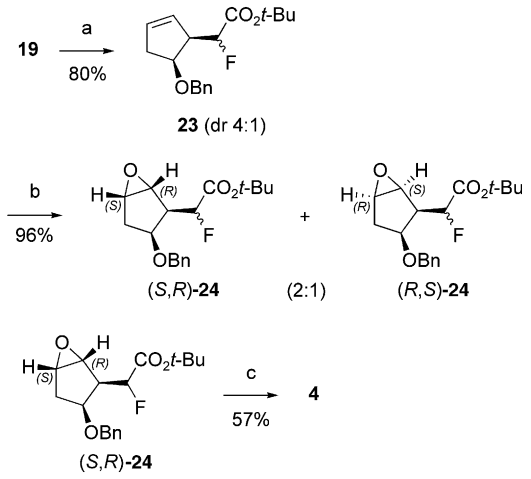
The synthesis of a similar ester was also achieved by a Johnson–Claisen rearrangement (Scheme 4). Alcohol **21** was prepared from **15** in two steps and treated with triethyl orthoacetate in the presence of hydroquinone as an acid catalyst.[24] The rearrangement proceeded at 140 °C to afford desired ethyl ester **22** in 46% overall yield (three steps).

Treatment of *tert*-butyl ester (**19**) with LDA and *N*-fluorobenzenesulfonimide afforded fluoro ester **23** in 80% yield as a mixture of diastereomers (4:1) (Scheme 5). Epoxidation of the mixture of diastereomers **23** with mCPBA proceeded with a diastereoselectivity of 2:1 to afford **24** in 96% combined yield as a mixture of four diastereomers (8:4:2:1). The diastereomers were separated by column chromatography, and the major isomer was subjected to the cyclization reaction. Treatment of (*S*,*R*)-**24** with LDA did not give bicyclic alcohol **4**. The starting material was recovered, however, as the other epimer with respect to the carbon–fluorine bond. This indicated that the deprotonation had occurred on this epoxy ester ((*SR*)-**24**) whereas amide **12** did not undergo deprotonation. This observation supports the stereoelectronic rationale discussed above (Fig. 2). When the resulting enolate was treated with Et_2AlCl, cyclization proceeded instantaneously to afford desired bicyclic alcohol **4** in 57% yield.[25]

In conclusion, we have achieved an enantioselective synthesis of a 2,4-dioxybicyclo[3.1.0]hexane-6-carboxylic acid ester and its 6-fluorinated derivative, which are



Scheme 4. Reagents and conditions: (a) TBSCl, imidazole, DMF, rt; (b) aq NaOH, MeOH, rt; (c) $CH_3C(OEt)_3$, hydroquinone (cat), 140 °C.



Scheme 5. Reagents and conditions: (a) LDA, $(PhSO_2)_2NF$, THF, −78 °C; (b) mCPBA, Na_2HPO_4, CH_2Cl_2, rt; then chromatographic separation of diastereomers; (c) LDA, Et_2AlCl, THF, −78 °C.

expected to be useful intermediates for the synthesis of mGluR group II agonists. Each synthetic route starts from enantiomerically pure materials that are commercially available. The non-fluorinated derivative was synthesized through an intramolecular displacement of a cyclic sulfite by an ester enolate. Whereas this process was not applicable to the construction of a monofluorinated cyclopropane ring, a Lewis acid–lithium amide base system was effective for the intramolecular cyclopropanation of an epoxy fluoro ester. Further studies on the cyclopropanation and its application to the synthesis of group II mGluR agonists will be reported separately in a full account.[17]

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