ORGANIC LETTERS

2004
Vol. 6, No. 21
3775−3777

Enantioselective Preparation of Ring-Fused 1-Fluorocyclopropane-1-carboxylate Derivatives: En Route to mGluR 2 Receptor Agonist MGS0028

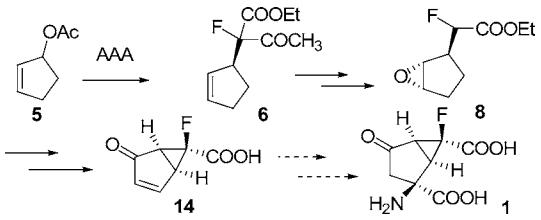
Fei Zhang,* Zhiguo J. Song, Dave Tschaen, and R. P. Volante

Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065

fei_zhang@merck.com

Received August 4, 2004

ABSTRACT



An approach to the densely functionalized fluorocyclopropane 14, a key framework toward the synthesis of mGluR 2 receptor agonist MGS0028 (1) is reported. The Trost AAA reaction enantioselectively introduced the key allylic stereogenic center and the α-fluoroester moiety. Stereoselective epoxidation followed by intramolecular epoxide ring opening efficiently constructed the 1-fluorocyclopropane-1-carboxylate matrix. This route can potentially be a general methodology for a concise, highly enantio- and stereoselective synthesis of 1-fluorocyclopropane-1-carboxylate derivatives.

MGS0028 (Figure 1), an mGluR 2 receptor agonist reported by the Taisho company,[1a] was shown to be potentially useful for targeting schizophrenia and anxiety. The goal of assembling this compound from an industrial process standpoint constitutes a significant challenge. MGS0028 resembles Lilly's LY354740[2] with elevated structural complexity, and both molecules possess a [3.1.0] fused ring system with an α-amino acid moiety. However, MGS0028 has not only numerous stereogenic centers along the fused ring systems but also a fluorine atom on the cyclopropane ring with defined stereochemistry.

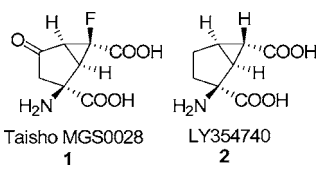


Figure 1. Structure of MGS0028 and Lilly's LY354740.

The original medicinal route[1] to MGS0028 features the enone **4** as a key intermediate derived from Saegusa oxidation[3] of ketone **3**, which itself was prepared as the racemic form by several low-yielding steps (<60% for multiple key steps) (Scheme 1). While the process of conversion of enone **4** to MGS0028 is well-established both at Merck and Taisho,[1] an enantioselective and scalable

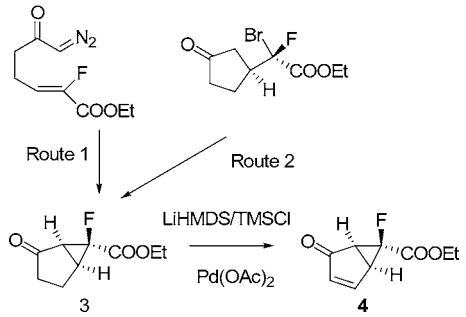
(1) (a) Nakazato, A.; Kumagai, T.; Sakagami, K.; Yoshikawa, R.; Suzuki, Y.; Chaki, S.; Ito, H.; Taguchi, T.; Nakanish, S.; Okuyama, S. *J. Med. Chem.* **2000**, *43*, 4893. (b) Tan, L.; Yasuda, N.; Yoshikawa, N.; Hartner, F. W.; Eng, K. K.; Leonard, W. R.; Tsay, F.-R.; Volante, R. P.; Tillyer, R. D. *J. Am. Chem. Soc.* Submitted in 2004.

(2) (a) Monn, J. A.; Valli, M. J.; Massey, S. M.; Wright, R. A.; Salhoff, C. R.; Johnson, B. G.; Howe, T.; Alt, C. A.; Rhodes, G. A.; Robey, R. L.; Griffey, K. R.; Tizzano, J. P.; Kallman, M. J.; Helton, D. R.; Schoepp, D. D. *J. Med. Chem*, **1997**, *40*, 528. (b) For synthetic studies, see: Moher, E. D. *Tetrahedron Lett.* **1996**, *37*, 48, 8637.

(3) , Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

10.1021/ol0484512 CCC: $27.50
Published on Web 09/11/2004

Scheme 1. Previous Route to MGS0028 Intermediate **4**

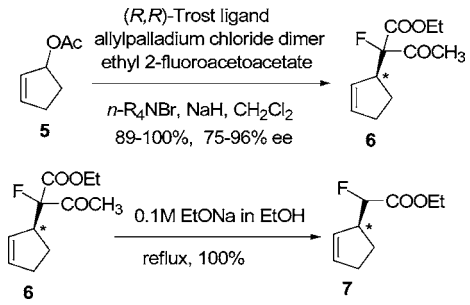


synthesis of enone **4** itself presents several daunting challenges such as limited reagent choices, toxic and costly fluorination reagents, and lack of convergency.

In the synthetic strategy reported here, we envisioned the Trost asymmetric allylic alkylation (AAA)[4] of commercially available and inexpensive ethyl 2-fluoroacetoacetate with cyclopentenyl acetate **5** as our key step to introduce the allylic chiral center and the fluorine atom. The second part of our strategy is to convert the olefin **7** to its *trans*-epoxide so that we can build the cyclopropane ring via intramolecular epoxide opening with the ester enolate.

Asymmetric Allylic Alkylation. To build the key allylic chiral center, we investigated the Trost AAA reaction of ethyl 2-fluoroacetoacetate with 2-cyclopentenyl acetate (Scheme 2). Following the standard Trost AAA protocol, only 75−

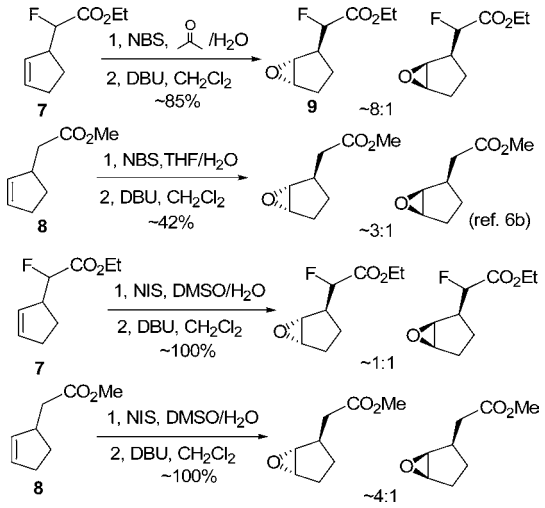
Scheme 2



81% ee (with respect to the allylic stereogenic center C*) was obtained with 5 mol % Pd loading and *n*-Bu_4NBr as a phase-transfer reagent. Decreasing Pd catalyst loading and using bulkier *n*-Hex_4N^+ counterion significantly improved the ee.[5] For example, when *n*-Hex_4NBr was chosen as the phase-transfer reagent, we observed 94−96% ee (89% yield) with 1 mol % Pd. Subsequently, to cleave the acetyl moiety, **6** was treated with 0.1 M ethanolic EtONa to afford **7**[6] in nearly quantitative yield. Overall, this sequence takes advantage of the well precedented Trost AAA reaction and obviates the use of much more toxic fluoroacetate.[7]

Epoxidation. To set up the stage for our intramolecular epoxide opening, it is mandatory that we find an efficient method to selectively form *trans*-epoxide **9**. A survey of the literature indicated that the epoxidation of substrates such as **7** strongly depends on solvents and epoxidation reagents.[8] Cis epoxides are generally favored with peroxy reagents due to the carbonyl directing effect,[8c] and our experiments confirmed the same trend. For example, both oxidation of **7** and **8** with *m*-CPBA or DMDO yielded mostly *cis*-epoxides, although reactions of **7** proceeded with a much slower reaction rate. The alternative halohydration−cyclization sequence, however, sometimes gives the opposite trans:cis selectivity, although the reported selectivities are only poor to moderate (~2.5:1 in the best case)[8a] and consequentially are rarely used. We found that under the halohydration conditions (Scheme 3), fluoroester **7** gave product distribu-

Scheme 3. Studies on Epoxidations of Esters **7** and **8**



tions remarkably different from those of nonfluoro substrate **8**. When ester **7** or **8** was treated sequentially with NBS and DBU, ester **7** gave higher trans selectivity. However, when NIS was used in place of NBS, ester **7** gave lower trans selectivity.[9] Furthermore, the rates of the halohydration reactions are significantly retarded by the presence of the fluorine atom. To the best of our knowledge, the ~8:1 trans:

(4) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089.

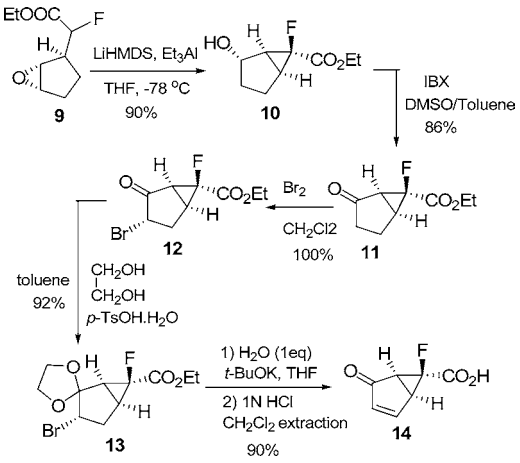
(5) Reaction with *n*-Bu_4NBr as a phase-transfer reagent gave 78−84% ee (94% yield) with 1 mol % Pd. However, when *n*-Hex_4NBr was used as the phase-transfer reagent, we observed 88−90% ee (90% yield) with 2 mol % Pd.

(6) Spectral data for olefin **7**: ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.85−5.95 (m, 1H), 5.55−5.65 (m, 1H), 4.60−4.90 (m, 1H), 4.15−4.30 (m, 2H), 3.10−3.30 (m, 1H), 2.25−2.50 (m, 2H), 1.70−2.10 (m, 2H), 1.25−1.35 (m, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm) −195.4, −196.5; ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 169.4, 169.3, 169.2, 169.1, 134.4, 128.5, 128.4, 127.95, 126.9, 91.9, 91.3, 90.0, 89.4, 61.3, 48.6, 48.4, 48.2, 32.1, 32.0, 25.05, 25.0, 23.9, 23.8, 14.1; IR neat cm^{-1} 3057, 2930, 1760; HRMS $[M + Li]^+$ calcud 178.1051, obsd 178.1055.

(7) Although both ethyl 2-fluoroacetoacetate and ethyl fluoromalonate are commercially available, the latter is about 10 times more expensive than the former. Furthermore, ethyl fluoroacetate is extremely toxic, and it is mandatory to handle this compound with special care.

(8) (a) Pearson, A. J.; Hsu, S.-Y. *J. Org. Chem.* **1986**, *51*, 2505. (b) Chung, C. K.; Kim, K.; Rhee, Y. H, Lee, H. *Bull. Korean Chem. Soc.* **1999**, *20* (1), 99. (c) Armstrong, A.; Barsanti, P.; Clarke, P. *Tetrahedron Lett.* **1994**, *35*, 6155.

Scheme 4



cis selectivity observed with **7** is far better than the selectivities previously reported with analogous substrates.[8] The epoxide **9** was used in the next step without purification. Upon treatment with Et_3Al and LiHMDS, epoxide **9** underwent clean intramolecular epoxide opening[10] to give alcohol **10** in excellent yield.[11] Oxidation of **10** with IBX[12] gave ketone **11**[13] smoothly.

Elimination. The conversion of ketone **11** to enone **14** has been known to be a challenging transformation, mostly because of the instability of enone **14**. For example, reaction of ketone **11** with IBX at 150 °C overnight in the mixed solvent of 2:1 toluene/DMSO suffered from low conversion (~40%) and severe decomposition. Although bromination of ketone **11** quantitatively afforded **12**, which could potentially serve as a candidate for dehydrobromination, exposure of bromoketone **12** to strong bases such as DBU and *t*-BuOK resulted only in fast decomposition of the substrate. A sluggish reaction was observed with $CaCO_3$ in refluxing DMF[14] to afford mostly unidentified aromatized species with the loss of fluorine atom.

Having realized that bromoketone **12** is not a well-behaved substrate for elimination to give enone **14**, we reasoned that **12** would have been much more maneuverable if the carbonyl group adjacent to the bromine bearing carbon had been protected. To test our hypothesis, bromoketone **12** was converted to ketal **13** under standard azeotropic ketalization conditions. In a small-scale reaction (~0.1 mmol), when ester **13** was treated with LDA or NaOEt in THF, quick saponification was observed and the resulting carboxylate strongly resisted further dehydrobromination. With *t*-BuOK, however, HBr elimination occurred and acid **14** was isolated in nearly pure form by simple acidic extraction. It is noteworthy that on a larger scale (~10 mmol), the reaction became irreproducible and low yielding even when 20 equiv of base was used, resulting in a black tar sometimes. We postulated that adventitious moisture might have been attributable to the success of dehydrobromination reactions in small scale. We also noted that hydrolysis of ethyl ester to carboxylate was much faster than dehydrobromination in all cases. In time, we were able to optimize the reaction by introducing 1 equiv of water to the THF solution of **13** prior to the addition of 5 equiv of base. Enone acid **14**[15] could be readily isolated in nearly quantitative yield by simple acidic extraction. Under aqueous basic conditions (0.1 N aqueous NaOH), **14** decomposed rapidly (within 2 h) yet it tolerated 0.1 N aqueous HCl overnight with less than 20% decomposition. Treatment of **14** with CH_2N_2 in benzene/MeOH gave rise to its methyl ester in 90% yield, and previous work[1] at Taisho has shown that the ethyl ester of enone **10** could be converted to the target MGS0028 in several steps.

In conclusion, a convergent route for the construction of the cyclopentane fused 1-fluorocyclopropane-1-carboxylate[16] ring system has been demonstrated. It features a stereoselective epoxidation and oxirane ring-opening strategy to construct the bicyclic ring system. This work overcomes some of the serious drawbacks of the previous routes such as lack of an asymmetric variant (rendered possible in our synthesis by stereospecificity of the AAA reaction) and employment of expensive and highly toxic fluorination reagents. The work reported herein will likely find application in enantioselective synthesis of other 1-fluorocyclopropane-1-carboxylate[16] derivatives present in other drug candidates.

Acknowledgment. Thomas Novak is gratefully acknowledged for HRMS analysis.

Supporting Information Available: Experimental procedures and full characterization data for **6**, **7**, and **10**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0484512

(9) Proton NMR spectra of *trans*- and *cis*-epoxides exhibit clear differences in chemical shift for the proton on the carbon with a branched fluoroester side chain. Due to a deshielding effect exerted by the epoxide oxygen, a downfield shift was observed for *trans*-epoxide. See ref 8a for analogous assignments and experimental for detailed spectroscopic data.

(10) (a) Babler, H.; Tortorello, A. J. *J. Org. Chem.* **1976**, *41*, 885. (b) Ficini, J.; d'Angelo, J. *Tetrahedron Lett.* **1976**, *28*, 2441. (c) Takano, S.; Sato, N.; Akiyama, M.; Ogasawara, K. *Heterocycles* **1985**, *23*, 2859. (d) An improved procedure for this transformation has been extensively studied by our department and will be reported in due course.

(11) Under this condition, a small amount of *cis*-epoxide present in the crude starting material yielded unidentified material associated with decomposition.

(12) IBX = 1-hydroxy-1,2-benziodoxal-3(1*H*)-one-1-oxide; see: Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S. *J. Am. Chem. Soc*. **2000**, *122*, 7596.

(13) Spectral data for ketone **11**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 4.23 (q, 2H, J = 7.2 Hz), 2.66−2.69 (m, 1H), 2.51−2.53 (m, 1H), 2.38−2.49 (m, 1H), 2.09−2.25 (m, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) δ (ppm) −211.2; ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 209.0, 167.2, 166.9, 81.0, 78.6, 62.5, 40.2, 40.1, 35.55, 35.5, 34.3, 34.1, 19.55, 19.5, 14.0; IR neat cm^{-1} 3070, 2984, 2894, 1731; HRMS [M + Li]$^+$ calcd 192.0844, obsd 192.0838.

(14) Green, G. F. H.; Long, A. G. *J. Chem. Soc.* **1961**, 2532.

(15) Spectral data for enone acid **14**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 10.7 (br, 1H), 7.46 (q, J = 5.4, 2.8 Hz, 1H), 6.08 (d, J = 5.5 Hz, 1H), 3.30 (q, J = 5.4, 2.8 Hz, 1H), 2.87 (d, J = 5.4 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ(ppm) −213.7; ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 200.0, 169.6, 169.3, 153.5, 133.3, 91.1, 88.6, 34.9, 34.8, 34.2, 34.1; IR neat (cm^{-1}) 3500(br), 3080, 2922, 2855, 1713; HRMS [M − H]$^+$ calcd 155.0145, observed 155.0145.

(16) (a) Saito, A.; Ito, H.; Taguchi, T. *Tetrahedron* **2001**, *57*, 7487. (b) For a review of fluorinated cyclopropanes, see: Battiste, M. A.; Dolbier, W. R., Jr. *Chem. Rev.* **2003**, *103*, 1071.