SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 11, pp. 1973–1980, 2004

A Ring Expansion Strategy in Antiviral Synthesis: A Novel Approach to TAK-779

Terrence L. Smalley Jr.*

GlaxoSmithKline, Inc., M&V CEDD Chemistry, Research Triangle Park, North Carolina, USA

ABSTRACT

A synthesis of TAK-779 that relies on construction of a key carboxylic acid intermediate by a ring expansion with $TMSCHN_2$ is described.

Key Words: Ring transformations; Amines; Suzuki reactions; Coupling reaction.

INTRODUCTION

Discovering effective medicines for the treatment of AIDS has long been a goal of the pharmaceutical industry. Current therapies include a cocktail of reverse transcriptase and protease inhibitors;[1] however, mutations of

*Correspondence: Terrence L. Smalley Jr., GlaxoSmithKline, Inc., M&V CEDD Chemistry, Five Moore Drive, , Research Triangle Park, North Carolina 27709, USA; Fax: (919) 315-0430; E-mail: terry.l.smalley@gsk.com.

DOI: 10.1081/SCC-120037909
Published by Marcel Dekker, Inc.
0039-7911 (Print); 1532-2432 (Online)
www.dekker.com

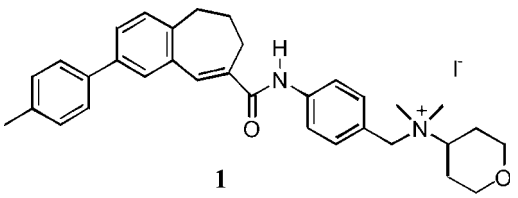
the HIV virus have resulted in resistance to conventional treatments.[1] Consequently, new and innovative treatments are sought that can treat patients who become resistant to classical anti-HIV therapeutics.

A recent publication disclosed a class of molecules that may potentially inhibit the progression of HIV by a novel mechanism involving antagonism of the CCR5 chemokine receptor.[2] In particular, TAK-779 **1** (Fig. 1) has shown excellent in vitro inhibition of the HIV virus, and its effectiveness as a treatment for HIV is currently being evaluated in the clinic. Because of our own interest in treating HIV, we sought to obtain **1** for use as an in-house research tool.

At the outset of this work no details regarding the synthesis of **1** had been described, although the details of the synthesis were disclosed upon completion of the present approach.[2] The original procedure initially used a Friedel–Crafts acylation reaction with bromobenzene to construct the 6,7-fused ring system. A lengthy sequence of functional group transformations was used to access key carboxylic acid **2**. Additionally, a process route to **1** employing a 12 step sequence has recently been reported starting from 4-(4-methylphenyl)benzonitrile.[3] The goal of the work presented here was to employ a short synthetic route to **2** avoiding the use of excess toxic reagents.

The retrosynthesis for the present work initiated with the obvious disconnection of the amide bond to give carboxylic acid **2** and amine **3** (Sch. 1). Carboxylic acid **2** could arise from suberone **4** by functional group modification. It was envisioned that **4** could arise from a suitably functionalized tetralone by simple ring expansion. For this reason, commercially available 7-methoxy-1-tetralone was chosen as the starting point in the synthesis.

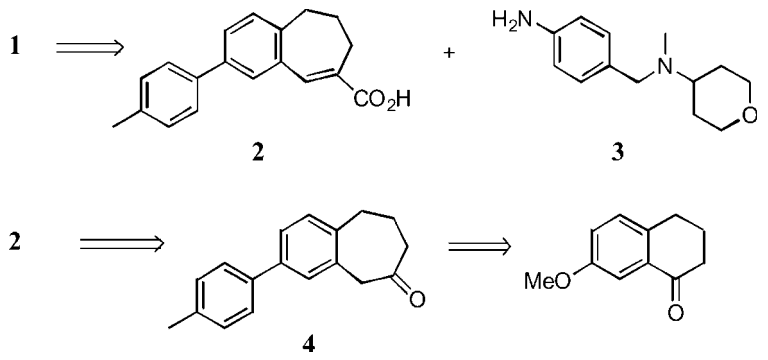
7-Methoxy-1-tetralone was elaborated to 7-(4-methylphenyl)-1-tetralone (**5**) by sequential demethylation with HBr,[4] conversion of the resulting phenol to the triflate with Tf_2O[5] and subsequent Suzuki coupling[2] with 4-methylbenzeneboronic acid (Sch. 2). Ring expansion of tetralone **5** was accomplished with trimethylsilyldiazomethane and $BF_3 \cdot OEt_2$[6] to provide the corresponding suberone **6** as a single regioisomer. The regiochemistry of the ring expansion was assigned on the basis of the ^1H NMR spectrum, which showed a singlet at δ 3.78 corresponding to the α-keto benzylic protons.



1

Figure 1. Structure of TAK-779 (**1**).

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016



Scheme 1.

Initial attempts to convert **6** to the vinyl triflate **7** were focused on the use of Tf_2O as the electrophile. Treatment of **6** with Tf_2O and Et_3N at 0°C led to a 10 : 1 mixture of the desired product **7** and its isomeric vinyl triflate in a combined 45% yield. Changing the base to Na_2CO_3 provided **7** in 59% yield as the sole product. Moreover, it was discovered the yields could be improved by changing the triflating reagent. Deprotonation of **7** with LiHMDS followed by quenching of the enolate with $PhNTf_2$[7] led to **7** in 60% yield. Alternatively, quenching of the enolate with 2-[*N*,*N*-*bis*(trifluoromethylsulfonyl)amino]-5-chloropyridine[8] led to **7** in a much improved 81% yield. The carboxylic acid moiety was installed by palladium mediated carbonylation[9] of **7** to provide α,β-unsaturated ester **8** in 77% yield. The key intermediate **2** was isolated upon saponification of **8**. The aniline **3**[2] was coupled to carboxylic acid **2** with EDC and HOBt to provide tertiary amine **11**. Reaction of **11** with excess CH_3I as reported[2] provided **1**.

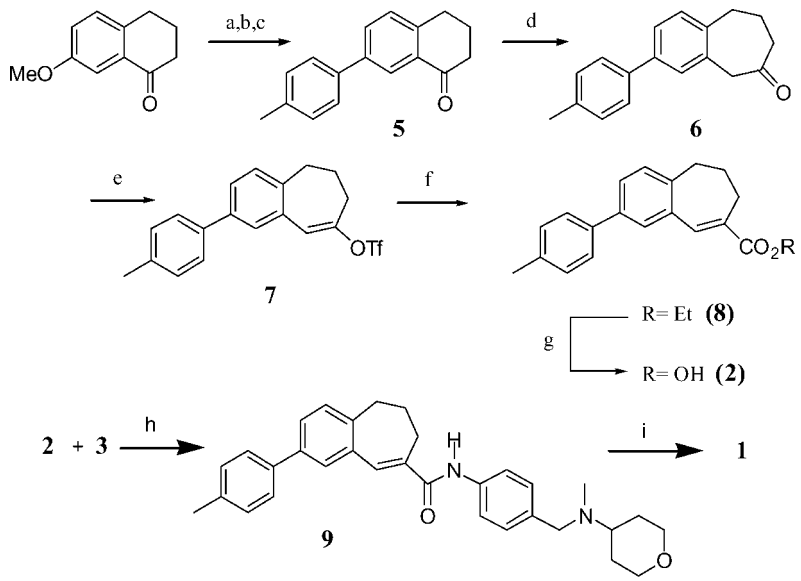
In summary, the discovery of **1** as a CCR5 inhibitor is a significant advance for the treatment of HIV infected patients. The synthesis of this exciting molecule was completed in nine linear steps from 7-methoxy-1-tetralone, a method which compares quite favorably with that described by previously.[2] The synthesis presented in this communication could be easily adapted for creating analogs of **1**.

EXPERIMENTAL SECTION

General

All chemicals and reagents were purchased from commercial sources except where noted and were used as received. Anhydrous THF, CH_2Cl_2,

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016



Scheme 2. (a) HBr/HOAc; (b) Tf_2O, Et_3N, CH_2Cl_2; (c) 4-methylphenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, $PhCH_3$, EtOH, H_2O, 110°C, 67% overall; (d) $BF_3 \cdot OEt_2$, Me_3SiCHN_2, 0°C, 47%; (e) LiHMDS, THF, −78°C then 2-[*N*,*N*-*bis*(trifluoromethylsulfonyl)amino]-5-chloropyridine, 81%; (f) CO, Et_3N, $PdCl_2(PPh_3)_2$, EtOH, 80°C, 77%; (g) LiOH, 4/1/1 THF/EtOH/H_2O, 78%; (h) EDC · HCl, HOBt, CH_2Cl_2, 50%; (i) CH_3I, DMF.

and toluene were purchased from Aldrich and used as received. Silica gel chromatography was performed on an Isco Sg100c single channel purification instrument using RediSep™ cartridges. NMR spectra were performed on Varian 400 and 300 MHz spectrophotometers. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab (Norcross, GA).

3-(4-Methylphenyl)-5,7,8,9-tetrahydro-6*H*-benzo[*a*][7]annulen-6-one (6). 7-(4-Methylphenyl)-3,4-dihydronaphthalen-1(2*H*)-one[2] (**5**, 7.93 g, 33.6 mmol) was suspended in Et_2O (34 mL) and cooled to 0°C under N_2. $BF_3 \cdot OEt_2$ (4.70 mL, 37.1 mmol) was added followed by dropwise addition of $TMSCHN_2$ (18.5 mL, 37.0 mmol). The mixture was stirred at 0°C for 45 min and sat. aq. $NaHCO_3$ (100 mL) was carefully added. The two layers were separated and the aqueous layer was extracted with Et_2O (2 × 25 mL). The organics were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel chromatography (RediSep™ 120 g cartridge, 85 : 15 hexane : EtOAc) to provide **6** as a yellow solid (3.99 g, 47%), mp = 82–83°C.

^{1}H NMR ($CDCl_3$): δ 7.46 (d, $J = 8.0$ Hz, 2H), 7.41 (dd, $J = 8.0$, 1.8 Hz, 1H), 7.4 (m, 1H), 7.22 (d, $J = 8.0$ Hz, 2H), 7.20 (d, $J = 8.0$ Hz, 1H), 3.78 (s, 2H), 2.97 (t, $J = 6.9$ Hz, 2H), 2.60 (t, $J = 6.9$ Hz, 2H), 2.38 (s, 3H), 2.0 (m, 2H) ppm. Elemental analysis calculated for $C_{18}H_{18}O$: C, 86.4%; H, 7.3%. Found: C, 86.31%; H, 7.22%.

2-(4-Methylphenyl)-6,7-dihydro-5*H*-benzo[*a*][7]annulen-8-yl trifluoromethanesulfonate (7). LiHMDS (13.6 mL, 13.6 mmol) was dissolved in THF (5 mL) and cooled to -78°C under N_2. A solution of 3-(4-methylphenyl)-5,7,8,9-tetrahydro-6*H*-benzo[*a*][7]annulen-6-one (**6**, 2.96 g, 11.8 mmol) in THF (6 mL) was added dropwise and the solution was stirred for 50 min. A solution of 5-chloro-2-*N*,*N*-*bis*(triflouromethyl)aminopyridine (4.83 g, 12.3 mmol) in THF (5 mL) was added and the mixture was stirred at -78°C for 60 min then at RT for 60 min. H_2O (15 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (2×10 mL). The organics were washed with 10% NaOH (25 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel chromatography (RediSep™ 40 g cartridge, 95 : 5 hexane : EtOAc) to provide the product as a colorless oil (3.67 g, 81%). ^{1}H NMR ($CDCl_3$): δ 7.50 (d, $J = 8.0$ Hz, 2H), 7.45 (dd, $J = 8.0$, 1.8 Hz, 1H), 7.4 (m, 1H), 7.28 (d, $J = 8.0$ Hz, 2H), 7.21 (d, $J = 8.0$ Hz, 1H), 6.69 (s, 1H), 2.96 (t, $J = 5.8$ Hz, 2H), 2.85 (t, $J = 6.5$ Hz, 2H), 2.43 (s, 3H), 2.1 (m, 2H) ppm. Elemental analysis calculated for $C_{19}H_{17}F_3O_3S$: C, 59.7%; H, 4.5%. Found: C, 59.82%; H, 4.46%.

Ethyl2-(4-methylphenyl)-6,7-dihydro-5*H*-benzo-[*a*][7]annulene-8-carboxylate (8). 2-(4-Methylphenyl)-6,7-dihydro-5*H*-benzo[*a*][7]annulen-8-yl trifluoromethanesulfonate (**7**, 3.67 g, 9.60 mmol) was dissolved in EtOH (15 mL). Et_3N (1.60 mL, 11.5 mmol) and $PdCl_2(PPh_3)_2$ (0.4178 g, 1.01 mmol) were added and the atmosphere was changed to CO (1 atm). The solution was heated to 80°C for 90 min then was cooled to RT and concentrated. The residue was purified by silica gel chromatography (RediSep™ 40 g cartridge, 9 : 1 hexane : EtOAc) to provide the product as a yellow oil (2.07 g, 70%). ^{1}H NMR ($CDCl_3$): δ 7.75 (s, 1H), 7.5 (m, 1H), 7.46 (d, $J = 8.0$ Hz, 2H), 7.41 (dd, $J = 8.0$, 1.8 Hz, 1H), 7.22 (d, $J = 8.0$ Hz, 2H), 7.18 (d, $J = 8.0$ Hz, 1H), 4.26 (q, $J = 7.1$ Hz, 2H), 2.82 (t, $J = 5.6$ Hz, 2H), 2.64 (t, $J = 6.5$ Hz, 2H), 2.37 (s, 3H), 2.1 (m, 2H), 1.34 (t, $J = 7.1$ Hz, 3H) ppm. Elemental analysis calculated for $C_{21}H_{22}O_2$: C, 82.3%; H, 7.2%. Found: C, 82.49%; H, 7.12%.

2-(4-Methylphenyl)-6,7-dihydro-5*H*-benzo-[*a*][7]annulene-8-carboxylic acid (2). Ethyl 2-(4-methylphenyl)-6,7-dihydro-5*H*-benzo-[*a*][7]annulene-8-carboxylate (**8**, 2.07 g, 6.76 mmol) was dissolved in THF (12 mL), EtOH (3 mL), and H_2O (3 mL). LiOH (0.8527 g, 20.3 mmol) was added and the solution was heated to 50°C for 24 hr. The mixture was cooled to RT and sat. aq.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

KH_2PO_4 (25 mL) was added. The mixture was extracted with Et_2O (4 × 10 mL) and the organics were dried (Na_2SO_4) and concentrated. The residue was triturated with hexane : Et_2O (9 : 1) to provide the product (1.18 g, 63%) as a pale yellow solid, mp = 184–186°C (dec.). ^{1}H NMR ($CDCl_3$): δ 7.90 (s, 1H), 7.54 (d, J = 1.4 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.44 (dd, J = 8.0, 1.8 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 1H), 2.87 (t, J = 5.5 Hz, 2H), 2.68 (t, J = 5.5 Hz, 2H), 2.38 (s, 3H), 2.1 (m, 2H) ppm. Elemental analysis calculated for $C_{19}H_{18}O_2 \cdot 0.15H_2O$: C, 81.2%; H, 6.6%. Found: C, 81.11%; H; 6.40%.

2-(4-Methylphenyl)-*N*-(4-{[methyl(tetrahydro-2H-pyran-4-yl)amino] methyl}phenyl)-6,7-dihydro-5*H*-benzo[*a*][7]annulene-8-carboxamide (9). 2-(4-Methylphenyl)-6,7-dihydro-5*H*-benzo-[*a*][7]annulene-8-carboxylic acid (**2**, 0.2015 g, 0.724 mmol) was dissolved in CH_2Cl_2 (1.40 mL) and cooled to 0°C. HOBt (0.1173 g, 0.868 mmol) and EDC · HCl (0.1668 g, 0.870 mmol) were added and the mixture was stirred for 40 min. TAK aniline (0.1600 g, 0.727 mmol) and (i-Pr)$_2$NEt (0.130 mL, 0.746 mmol) were added and the mixture was warmed to RT and stirred for 2 hr. H_2O (15 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The organics were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel chromatography (9 : 1 CH_2Cl_2 : MeOH) to provide the product (0.1740 g, 50%) as a white solid, which was used without further purification. ^{1}H NMR ($CDCl_3$): δ 7.67 (s, 1H), 7.57 (d, J = 8.0 Hz, 2H) 7.50 (d, J = 1.4 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.41 (dd, J = 8.0, 1.8 Hz, 1H), 7.4 (m, 2H), 7.20 (d, J = 8.0 Hz, 2H), 4.02 (dd, J = 11.0, 3.8 Hz, 2H), 3.64 (s, 2H), 3.34 (dt, J = 11.7, 1.8 Hz, 2H), 2.86 (t, J = 8.6 Hz, 2H), 2.7 (m, 1H), 2.69 (t, J = 6.3 Hz, 2H), 2.37 (s, 3H), 2.25 (s, 3H), 2.1 (m, 2H), 1.8 (m, 2H), 1.7 (m, 2H) ppm. LRMS calcd for $C_{32}H_{36}N_2O_2$: m/z = 480. Found: m/z = 481 ($M + H^+$).

***N*,*N*-Dimethyl-*N*-[4-({[2-(4-methylphenyl)-6,7-dihydro-5*H*-benzo[*a*] [7]annulen-8-yl]carbonyl}amino)benzyl]tetrahydro-2*H*-pyran-4-aminium iodide (1).** 2-(4-Methylphenyl)-*N*-(4-{[methyl(tetrahydro-2H-pyran-4-yl) amino]methyl}phenyl)-6,7-dihydro-5*H*-benzo[*a*][7]annulene-8-carboxamide (**9**, 0.1210 g, 0.252 mmol) was dissolved in DMF (8 mL). CH_3I (0.100 mL, 1.61 mmol) was added and the mixture was stirred at RT overnight. The mixture was concentrated and the residue was triturated with EtOAc. The solid was recrystallized from EtOAc/EtOH (3 : 1) to provide the product as a yellow solid. ^{1}H NMR (d_6-DMSO): δ 10.18 (s, 1H), 7.82 (d, J = 8.5 Hz, 2H), 7.63 (s, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.32 (s, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 4.41 (s, 2H), 4.00 (dd, J = 11.0, 1.8 Hz, 2H), 3.53 (t, J = 1.8 Hz, 1H), 2.83 (s, 6H), 2.81 (t, J = 6.0 Hz, 2H), 2.60 (t, J = 6.0 Hz, 2H), 2.30 (s, 3H), 2.12 (d, J = 11.0 Hz, 2H), 2.0 (m, 2H), 1.8 (m, 2H) ppm. Elemental analysis for

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

$C_{33}H_{39}IN_2O_2 \cdot 3H_2O$: C, 58.56%; H, 6.71%; N, 4.14%. Found: C, 58.62%; H, 6.34%; N, 4.55%. LRMS calcd for $C_{33}H_{39}N_2O_2$: $m/z = 496$. Found: $m/z = 496$.

ACKNOWLEDGMENTS

The author would like to thank Mr. Virgil L. Styles, Dr. Wieslaw Kazmierski, and Dr. Paul Feldman for informative discussions during the course of this work and for critical reading of this manuscript.

REFERENCES

1. (a) Corbett, J.W.; Ko, S.S.; Rodgers, J.D.; Jeffrey, S.; Bacheler, L.T.; Klabe, R.M.; Diamond, S.; Lai, C.-M.; Rabel, S.R.; Saye, J.A.; Adams, S.P.; Trainor, G.L.; Anderson, P.S.; Erickson-Viitanen, S.K. Expanded spectrum nonnucleoside reverse transcriptase inhibitors inhibit clinically relevant mutant variants of human immunodeficiency virus type I. Antimicrob. Agents Chemother. **1999**, *43*, 2893–2897; (b) Hopkins, A.L.; Ren, J.; Tanaka, H.; Baba, M.; Okamato, M.; Stuart, D.I.; Stammers, D.K. Design of MKC-442 (emivirine) analogs with improved activity against drug-resistant HIV mutants. J. Med. Chem. **1999**, *42*, 4500–4505 (and references therein).
2. (a) Shiraishi, M.; Aramaki, Y.; Seto, M.; Imoto, H.; Nishikawa, Y.; Kanzaki, N.; Okamoto, M.; Sawada, H.; Nishimura, O.; Baba, M.; Fujino, M. Discovery of novel, potent and selective small molecule CCR5 anatgonists as anti-HIV-1 agents: synthesis and biological evaluation of anilide derivatives with a quaternary ammonium moiety. J. Med. Chem. **2000**, *43*, 2049–2063; (b) Baba, M.; Nishimura, O.; Kanzaki, N.; Okamato, M.; Sawada, H.; Iizawa, Y.; Shiraishi, M.; Aramaki, Y.; Okonogi, K.; Ogawa, Y.; Meguro, K.; Fujino, M. A small molecule nonpeptide CCR5 antagonist with highly potent and selective anti-HIV-1 activity. Proc. Natl. Acad. Sci. USA **1999**, *96*, 5698–5703; (c) Nishimura, O.; Baba, M.; Sawada, H.; Kanzaki, N.; Kuroshima, K.; Shiraishi, M.; Aramaki, Y. Pharmaceutical Composition for Antagonizing CCR5 Comprising Anilide Derivative. Patent #WO 99/32100, July 1, 1999.
3. Ikemoto, T.; Ito, T.; Hashimoto, H.; Kawarasaki, T.; Nishiguchi, A.; Mitsudera, H.; Wakimasu, M.; Tomimatsu, K. Development of a new synthetic route of a non-peptide CCR5 anatgonist, TAK-779, for large scale preparation. Org. Process Res. Dev. **2000**, *4*, 520–525.

4. Mosettig, E.; May, E.L. Tetrahydroisoquinolino alcohols derived from tetrahydronaphthalene. J. Org. Chem. **1940**, *5*, 528–543.
5. Stang, P.J.; Hanack, M.; Subramanian, L.R. Perfluoroalkanesulfonic esters: methods of preparation and applications in organic chemistry. Synthesis **1982**, 85–126.
6. Hashimoto, N.; Aoyama, T.; Shiori. New methods and reagents in organic synthesis. 18. Homologation of ketones with trimethylsilyldiazomethane. T. Chem. Pharm. Bull. **1982**, *30*, 119–124.
7. McMurry, J.E.; Scott, W.J. A method for the regiospecific of enol triflates by enolate trapping. Tetrahedron. Lett. **1983**, *24*, 979–982.
8. Comins, D.L.; Dehghani, A. Pyridine-derived triflating reagents: an improved preparation of vinyl triflates from metallo enolates. Tetrahedron. Lett. **1992**, *33*, 6299–6302.
9. Ritter, K. Synthetic transformation of vinyl and aryl triflates. Synthesis **1993**, 735–762.

Received in the USA January 6, 2004

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016