ORGANIC LETTERS

2011
Vol. 13, No. 5
952–955

Enantioselective Synthesis of a GPR40 Agonist AMG 837 via Catalytic Asymmetric Conjugate Addition of Terminal Alkyne to α,β-Unsaturated Thioamide

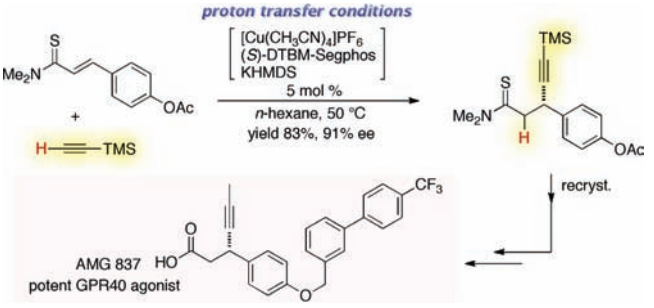
Ryo Yazaki,[†,‡] Naoya Kumagai,[*,†] and Masakatsu Shibasaki[*,†]

Institute of Microbial Chemistry, Tokyo, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan, and Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

nkumagai@bikaken.or.jp; mshibasa@bikaken.or.jp

Received December 10, 2010

ABSTRACT



A concise enantioselective synthetic route to a potent GPR40 agonist AMG 837 is described. The crucial catalytic asymmetric conjugate addition of terminal alkyne was promoted by a soft Lewis acid/hard Brønsted base cooperative catalyst, allowing efficient construction of the requisite stereogenic center. The thioamide functional group is key to both activation in asymmetric alkynylation and facile transformation into carboxylic acid.

The G-protein coupled receptor GPR40 was regarded as an orphan receptor until the discovery of its endogenous agonists, free fatty acids that amplify insulin secretion from pancreatic β-cells,[1−3] indicating that GPR40 agonists and antagonists are potential therapeutic targets for insulin-involved disorders such as type 2 diabetes.[4] Recently, a β-alkynyl acid derivative AMG 837 (**1**) was identified as a potent GPR40 agonist at Amgen.[5]

[†] Institute of Microbial Chemistry, Tokyo.
[‡] Graduate School of Pharmaceutical Sciences, The University of Tokyo.

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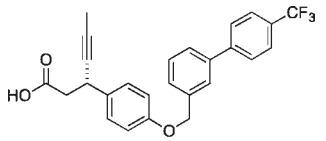
10.1021/ol102998w
Published on Web 02/03/2011



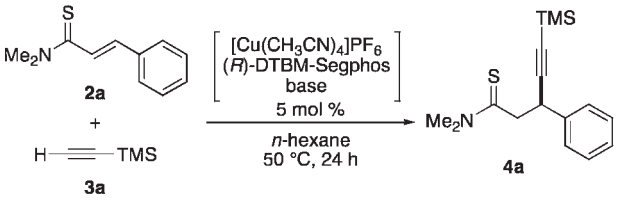
AMG 837 (1)

potent GPR40 agonist

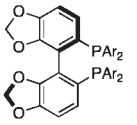
The first generation synthetic route to **1** developed by Amgen relied on optical resolution to provide enantiopure samples for toxicologic and clinical studies. Subsquently, Cui and Walker at Amgen established a reliable and scalable enantioselective synthesis of **1** through asymmetric conjugate addition of an alkynyl Grignard reagent to Meldrum's acid-derived acceptors.[6] Although this second generation route advanced the synthetic efficiency, the use of more than stoichiometric amounts of cinchonidine, Me_2Zn, and propynylmagnesium chloride is essential to construct the requisite stereogenic center with high yield and excellent enantioselectivity, and there remains room for further improvement.

Catalytic asymmetric conjugate addition of terminal alkynes to α,β-unsaturated carboxylates offers the most straightforward and efficient access to the optically active β-alkynyl acid derivatives,[7] but few methods exist for this transformation in a catalytic asymmetric manner, likely due to the diminished reactivity of in situ generated transition metal alkynylides. Recently, to address this issue, our group focused on the simultaneous activation of both a terminal alkyne and an acceptor to compensate for the low reactivity of the transition metal alkynylide. α,β-Unsaturated thioamides[8,9] were selected as suitable acceptors to engage the enantioselective coupling with terminal alkynes, in which the Lewis basic nature of both the alkyne and thioamide functional groups was exploited for simultaneous activation by a soft Lewis acid/hard Brønsted base

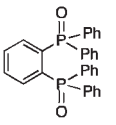
Table 1. Direct Catalytic Asymmetric Conjugate Addition of TMS Acetylene **3a**[a]



entry	**3a** (equiv)	base	yield[b] (%)	ee (%)
1[c]	2	Li(OC$_6$H$_4$-*p*-OMe)	trace	—
2	2	LiHMDS	32	89
3	2	NaHMDS	59	88
4	2	KHMDS	74	92
5	5	KHMDS	85[d]	91



(*R*)-DTBM-Segphos (*R*)-**5**
Ar = 3,5-^{t}Bu$_2$-4-MeO-C$_6$H$_2$



phosphine oxide **6**

[a] **2a**, 0.2 mmol. [b] Determined by ^{1}H NMR of the crude mixture with 2-methoxynaphthalene as an internal standard. [c] 10 mol % of phosphine oxide **6** was used. [d] Isolated yield.

cooperative catalyst. Based on this strategy, we developed a direct catalytic asymmetric conjugate addition of terminal alkynes to α,β-unsaturated thioamides that proceeds under proton transfer conditions.[10] Herein we report a concise enantioselective synthesis of AMG 837 (**1**) via soft Lewis acid/hard Brønsted base catalyzed[11] asymmetric conjugate addition of a terminal alkyne to α,β-unsaturated thioamide.

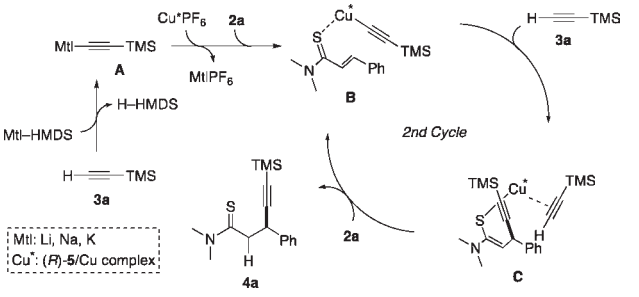


Figure 1. Proposed catalytic cycle with Mtl-HMDS.

We began our studies using silyl acetylene as an acetylene equivalent in the direct catalytic asymmetric conjugate

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(7) For copper catalyzed asymmetric conjugate additions of terminal alkynes, see: (a) Knöpfel, T. F.; Carreira, E. M. *J. Am. Chem. Soc.* **2003**, *125*, 6054. (b) Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 9682. (c) Fujimori, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4964. For rhodium catalyzed asymmetric conjugate additions of terminal alkynes, see: (d) Nishimura, T.; Guo, X.-X.; Uchiyama, N.; Katoh, T.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 1576. (e) Nishimura, T.; Tokuji, S.; Sawano, T.; Hayashi, T. *Org. Lett.* **2009**, *11*, 3222. (f) Nishimura, T.; Sawano, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 8057. (g) Fillion, E.; Zorzitto, A. K. *J. Am. Chem. Soc.* **2009**, *131*, 14608. (h) Nishimura, T.; Sawano, T.; Tokuji, S.; Hayashi, T. *Chem. Commun.* **2010**, *46*, 6837. For the catalytic asymmetric conjugate addition of preactivated terminal alkynes, see: (i) Kwak, Y.-S.; Corey, E. J. *Org. Lett.* **2004**, *6*, 3385. (j) Wu, T. R.; Chong, J. M.; Corey, E. J. *Org. Lett.* **2010**, *12*, 300.

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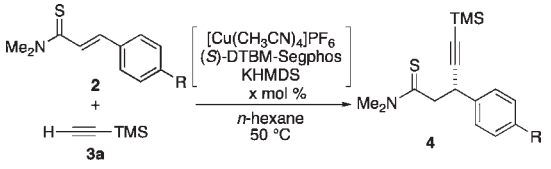
(9) For utility of thioamide functional group, see: Jagodziński, T. S. *Chem. Rev.* **2003**, *103*, 197.

(10) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 10275.

(11) (a) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837. (b) Suto, Y.; Tsuji, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 3757. (c) Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 14556. For CuO^{t}Bu-catalyzed 1,2-addition of terminal alkynes, see: (d) Motoki, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 2997. (e) Asano, Y.; Hara, K.; Ito, H.; Sawamura, M. *Org. Lett.* **2007**, *9*, 3901.

addition to install the propyne unit of **1**. Initial investigation revealed that the previously developed catalytic system comprising $[Cu(CH_3CN)_4]PF_6$, (*R*)-DTBM-Segphos (*R*)-**5**,[12] $Li(OC_6H_4$-*p*-OMe), and bisphosphine oxide **6**[13] was less effective in an attempted reaction of α,β-thioamide **2a** and TMS acetylene **3a**, likely because nucleophilic addition of in situ generated Cu acetylide was hampered by the increased steric demand of **3a** (Table 1, entry 1). We envisioned using a catalytic amount of a stronger base, LiHMDS, to generate Li acetylide **A** efficiently, which would give Cu acetylide **B** through transmetalation (Figure 1). Subsequently, enantioselective conjugate addition of Cu acetylide to Cu-activated **2a** likely proceeds to give Cu thioamide enolate **C**,[14] which then would function as a Brønsted base to drive the next catalytic cycle and liberate the desired product **4a**.[15] The HMDS-type base of a more electropositive alkali metal exhibited higher catalytic efficiency (entries 2−4), affording **4a** in 74% yield with 92% ee with KHMDS (entry 4).[16] The yield was further improved by using 5 equiv of **3a** (entry 5).[17]

Table 2. Direct Catalytic Asymmetric Conjugate Addition to α,β-Unsaturated Thioamides Bearing a *p*-Oxy Substituent[a]



entry	R	2	*x*	product	time (h)	yield[b] (%)	ee (%)
1	OMe	**2b**	10	**4b**	18	trace	—
2	OAc	**2c**	10	**4c**	18	58	92
3	OPiv	**2d**	10	**4d**	18	31	—
4	OMs	**2e**	10	**4e**	18	ND	—
5	OAc	**2c**	10	**4c**	40	80	90
6	OAc	**2c**	5	**4c**	40	83[c]	91

[a] **2**, 0.2 mmol; **3a**, 1.0 mmol. [b] Determined by ^1H NMR of the crude mixture with 2-methoxynaphthalene as an internal standard. [c] Isolated yield.

Having established the reaction conditions for TMS acetylene **3a** as the pronucleophile, β-aryl-α,β-unsaturated thioamides bearing a *p*-oxy substituent were investigated for the synthesis of **1** (Table 2). The reaction efficiency was significantly different depending on the electronic character of the *p*-oxy substituent. Substrate **2b**, with an electron-donating *p*-OMe group, afforded only trace amounts of the corresponding coupling product **4b**, even with a 10 mol % catalyst loading, presumably due to attenuated reactivity compared with nonsubstituted substrate **2a** (Table 2, entry 1 vs Table 1, entry 5). In contrast, α,β-unsaturated thioamide **2a** with an electron-withdrawing *p*-OAc group afforded product **4c** in moderate yield with 92% ee (entry 2), which proved to be better than that obtained from the analogous substrate bearing a *p*-OPiv group (entry 3). Unexpectedly, a more electron-withdrawing *p*-OMs substituent did not afford the desired product (entry 4).[18] Further optimization of the reaction conditions using **2c** revealed that a higher concentration and extended reaction time contributed to give a higher yield (entry 5), and the catalyst loading could be reduced to 5 mol % to afford **4c** in 83% yield with 91% ee (entry 6). The absolute configuration of **4c** prepared by using (*S*)-DTBM-Segphos (*S*)-**5** was determined to be *S* by X-ray crystallographic analysis (Figure 2).[19]

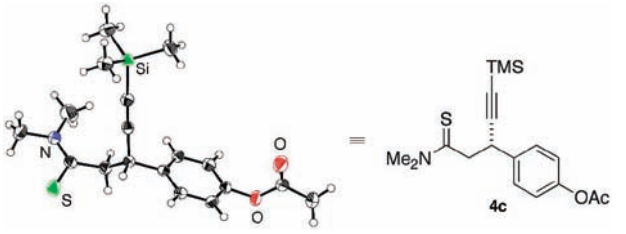


Figure 2. X-ray crystal structure of **4c**.

Due to the highly crystalline nature of **4c**, enantioenrichment was easily conducted in a CH_2Cl_2/*n*-hexane binary solvent system to provide an enantiopure sample (> 99% ee) in 84% yield (Scheme 1). With enantiopure **4c** bearing the requisite stereogenic center of **1** in hand, we focused on the enantioselective synthesis of **1**. Facile conversion of a thioamide functional group into the thioester was conducted by treatment with MeI in the presence of H_2O under acidic conditions, giving the corresponding thioester **7**.[20] Without purification, **7** was subjected to Cs_2CO_3/MeOH to remove the TMS group and acetyl group as well as to transform the thioester to methyl ester to afford **8**. Ether

(12) (a) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264. (b) Shimizu, H.; Nagasaki, I.; Matsumura, K.; Sayo, N.; Saito, T. *Acc. Chem. Res.* **2007**, *40*, 1385.

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(14) An attempted reaction of **2a** and the Li acetylide of **3a** prepared from a stoichiometric amount of ^{n}BuLi did not afford **4a** in the absence of a Cu complex even at 50 °C, suggesting that transmetalation to Cu acetylide is likely involved. Indeed, the reaction proceeded smoothly with 5 mol % of a mesitylcopper/(*R*)-DTBM-Segphos catalyst, where only the Cu acetylide of **3a** can be formed, affording **4a** in 91% yield and 90% ee under otherwise identical conditions.

(15) The possibility that H-HMDS was deprotonated by intermediate **C** and the resultant Cu-HMDS functions as a Brønsted base for the next catalytic cycle cannot be ruled out. Considering the proximity of **3a** and Cu thioamide enolate in intermediate **C**, the direct deprotonation as depicted in Figure 1 is more likely.

(16) With a $Li(OC_6H_4$-*p*-OMe) base (entry 1), retarded nucleophilic addition would cause reprotonation of Cu acetylide by in situ generated HOC_6H_4-*p*-OMe, leading to low catalytic performance. The higher catalytic efficiency by using KHMDS is not clear at this stage.

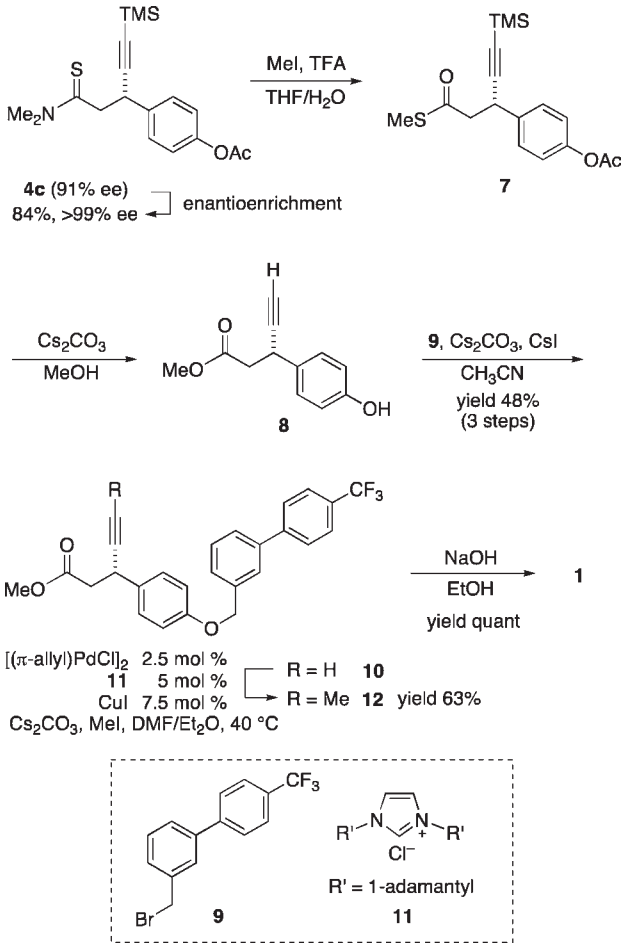
(17) Sterically bulkier TES acetylene instead of TMS acetylene gave an inferior result (63% yield, 92% ee). Even bulkier TBS or TIPS acetylenes did not afford any product presumably due to considerable steric repulsion in the transition state. The reaction using propyne was not reproducible and is under investigation.

(18) A thioamide bearing a β-*p*-trifluoroacetoxyphenyl substituent was unstable and readily hydrolyzed.

(19) See Supporting Information for details.

(20) Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron* **1999**, *55*, 1187.

Scheme 1. Enantioselective Synthesis of **1**



formation of the resultant crude material containing **8** and **9** under basic conditions afforded terminal alkyne **10** in 48% yield in three steps. Installation of the methyl group at the terminal alkyne was performed by Sonogashira coupling with MeI using carbene precursor **11** to provide **12** in 64% yield.[21,22] Basic hydrolysis of **12** delivered **1**, a potent GPR40 agonist.

In conclusion, we developed an enantioselective synthetic route to a potent GPR40 agonist **1** via direct catalytic asymmetric conjugate addition of a terminal alkyne to an α,β-unsaturated thioamide. The initial formation of an alkali metal acetylide with catalytic amounts of strong base is key to using TMS acetylene, and the intermediate Cu thioamide enolate served as base in the following catalytic cycle. The facile transformation of a thioamide functional group to a carboxylic acid derivative allowed efficient access to **1**. Further application of the present alkynylation method to the catalytic asymmetric synthesis of biologically active compounds is now ongoing.

Acknowledgment. This work was financially supported by a Grant-in-Aid for Scientific Research (S) (M.S.) and the Sumitomo Foundation (N.K.). R.Y. is thankful for a JSPS predoctral fellowship. Dr. Motoo Shiro at Rigaku Corporation is gratefully acknowledged for X-ray crystallographic analysis of **4c**.

Supporting Information Available. Characterization of new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642.
(22) No racemization was observed at this stage as confirmed by chiral-stationary-phase HPLC analysis.