ORGANIC LETTERS

2007
Vol. 9, No. 20
4029−4032

Catalytic Activation of the Leaving Group in the S_N2 Reaction§

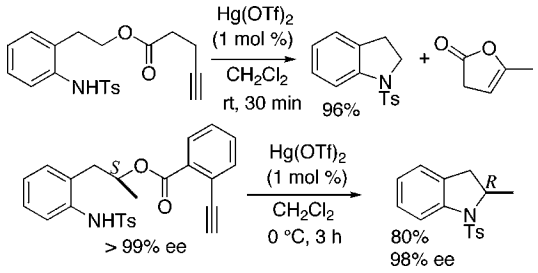
Hirofumi Yamamoto, Ghanshyam Pandey, Yumiko Asai, Mayo Nakano, Atsushi Kinoshita, Kosuke Namba, Hiroshi Imagawa, and Mugio Nishizawa*

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan

mugi@ph.bunri-u.ac.jp

Received July 20, 2007

ABSTRACT



A novel catalytic activation of the leaving group in the S_N2 reaction is achieved as an extension of our mercuric triflate-catalyzed reactions. Derivatives of anilinoethyl 4-pentynoate reacted smoothly with catalytic amounts of $Hg(OTf)_2$ to give indoline derivatives in excellent yield with efficient catalytic turnovers under very mild conditions. The reaction of optically pure secondary alcohol derivatives resulted in inversion of stereochemistry, which is a definitive feature of the S_N2 reaction. The procedure is applicable for benzoazepine synthesis.

The S_N2 reaction is a single-step reaction via a transition state as formulated by Hughes and Ingold in 1937, and it is a principal backbone of organic chemistry.[1] Mitsunobu developed the second generation of S_N2 reactions of alcohol using diethylazodicarboxylate, benzoic acid, and triphenylphosphine, the so-called Mitsunobu reaction.[2,3] So far, the S_N2 reaction has been recognized as a stoichiometric bimolecular reaction between a nucleophile and a substrate. Herein we report a novel catalytic activation of the leaving group for the S_N2 reaction as an extension of our original mercury(II) trifluoromethanesulfonate [hereafter $Hg(OTf)_2$]-catalyzed reactions.[4,5] Recently, we found that the $Hg(OTf)_2$ complex showed highly efficient catalytic activity based upon a significant affinity for the alkynyl group as well as an efficient protodemercuration sequence resulting in regeneration of $Hg(OTf)_2$.[6] We found that the $Hg(OTf)_2$·tetra-

§ In memory of the late Professor Yoshihiko Ito.

(1) (a) Cowdrey, W. A.; Hughes, E. D.; Ingold, C. K. *Nature* **1936**, *138*, 759. (b) Hughes, E. D.; Ingold, C. K.; Scott, A. D. *J. Chem. Soc.* **1937**, 1201−1208. (c) Hughes, E. D.; Ingold, C. K.; Martin, L. R. J.; Meigh, D. F. *Nature* **1950**, *166*, 679−680.

(2) (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380−2382. (b) Mitsunobu, O. *Synthesis* **1981**, 1−28.

(3) (a) Tsunoda, T.; Yamamiya, Y.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 1639−1642. (b) Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Ito, S. *Chem. Lett.* **1994**, 539−542. (c) Tsunoda, T.; Ozaki, F.; Ito, S. *Tetrahedron Lett.* **1994**, *35*, 5081−5082. (d) Tsunoda, T.; Yamamiya, Y.; Kawamura, Y.; Ito, S. *Tetrahedron Lett.* **1995**, *36*, 2529−2530. (e) Tsunoda, T.; Nagino, C.; Oguri, M.; Ito, S. *Tetrahedron Lett.* **1996**, *37*, 2459−2462.

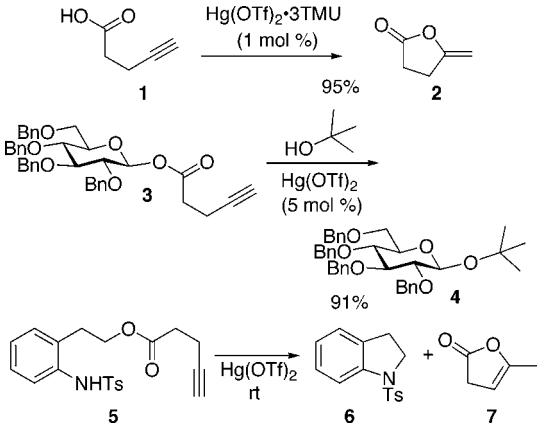
(4) (a) Nishizawa, M.; Takenaka, H.; Nishide, H.; Hayashi, Y. *Tetrahedron Lett.* **1983**, *24*, 2581−2584. (b) Nishizawa, M.; Morikuni, E.; Asoh, K.; Kan, Y.; Uenoyama, K.; Imagawa, H. *Synlett* **1995**, 169−170. (c) Nishizawa, M. *Studies in Natural Product Chemistry*.; Vol. 1, Stereoselective Synthesis, Part A; Rahman, A. u., Ed.; Elsevier: Amsterdam, Holland, 1988; pp 655−676. (d) Nishizawa, M. *J. Syn. Org. Chem. Jpn.* **1999**, *57*, 677−688. (e) Nishizawa, M.; Imagawa, H. *J. Syn. Org. Chem. Jpn.* **2006**, *64*, 744−751.

(5) (a) Nishizawa, M.; Takenaka, H.; Hirotsu, K.; Higuchi, T.; Hayashi, Y. *J. Am. Chem. Soc.* **1984**, *106*, 4290−4291. (b) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Am. Chem. Soc.* **1985**, *107*, 522−523. (c) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1986**, *51*, 806−813. (d) Nishizawa, M.; Yamada, H.; Hayashi, Y. *Tetrahedron Lett.* **1986**, *27*, 187−190. (e) Nishizawa, M.; Yamada, H.; Hayashi, Y. *J. Org. Chem.* **1987**, *52*, 4878−4884. (f) Nishizawa, M.; Takao, H.; Kanoh, N.; Asoh, K.; Hatakeyama, S.; Yamada, H. *Tetrahedron Lett.* **1994**, *35*, 5693−5696. (g) Nishizawa, M.; Morikuni, E.; Takeji, M.; Asoh, K.; Hyodo, I.; Imagawa, H.; Yamada, H. *Synlett* **1996**, 927−928. (h) Nishizawa, M.; Takao, H.; Iwamoto, Y.; Yamada, H.; Imagawa, H. *Synlett* **1998**, 76−78. (i) Nishizawa, M.; Imagawa, H.; Hyodo, I.; Takeji, M.; Morikuni, E.; Asoh, K.; Yamada, H. *Tetrahedron Lett.* **1998**, *39*, 389−392.

10.1021/ol701737x CCC: $37.00
Published on Web 09/01/2007

methylurea (hereafter TMU)-catalyzed cyclization of alky--noic acid **1** to γ-methylene-γ-lactone **2** is extremely rapid,[7a] and we used the alkynoic acid residue as the leaving group for $Hg(OTf)_2$-catalyzed glycosylations such as **3** to **4**, i.e., the typical S_N1 reaction.[7b] Now, we have turned our attention to the $Hg(OTf)_2$-catalyzed S_N2 reaction using the alkynoic acid residue as the leaving group. An anilinoethanol derivative **5** was designed as a substrate, which underwent a novel catalytic S_N2 reaction that generated indoline **6** in high yield with excellent catalytic turnover under very mild reaction conditions. We also found that the $Hg(OTf)_2$-catalyzed S_N2 reaction of the optically pure secondary alcohol derivative (*S*)-**16** proceeded with inversion of configuration to give (*R*)-**13** in >99% ee. Furthermore, the procedure was shown to be applicable to the syntheses of tetrahydroquinoline, tetrahydrobenzoazepin, and chroman.

Scheme 1. $Hg(OTf)_2$-Catalyzed Reactions



Reactions of 4-pentynoate **5** with 5 and 1 mol % of $Hg(OTf)_2$ (prepared in CH_3CN and employed as CH_3CN solutions) were examined in various solvents such as CH_3CN, MeO-*t*-Bu, CH_3NO_2, $C_6H_5CH_3$, $(CH_2Cl)_2$, and CH_2Cl_2, at 25 °C for 30 min (Table 1). The optimum conditions were found to be using 1 mol % of $Hg(OTf)_2$ and CH_2Cl_2 giving rise to indoline **6**[8] in 96% yield (Table 1, entry 10). Enol lactone **7** was identified in the NMR spectrum of the crude extract by comparison with authentic

Table 1. $Hg(OTf)_2$-Catalyzed S_N2 Reaction of **5** To Give **6**

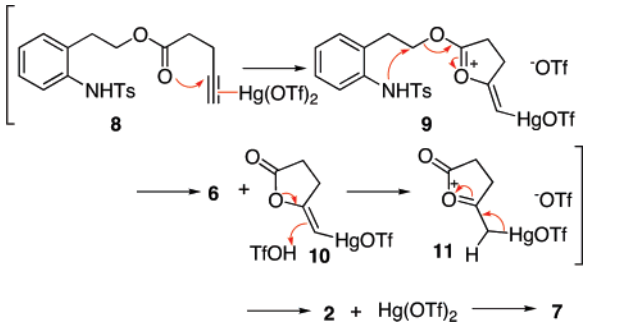
entry	$Hg(OTf)_2$ (mol %)	solvent	time (h)	yield (%)[a] **6**	**5**
1	5	CH_3CN	0.5	10	62
2	5	MeO-*t*-Bu	0.5	8	53
3	5	CH_3NO_2	0.5	90	-
4	1	CH_3NO_2	24	trace	94
5	5	$C_6H_5CH_3$	0.5	88	
6	1	$C_6H_5CH_3$	0.5	trace	96
7	5	$(CH_2Cl)_2$	0.5	96	
8	1	$(CH_2Cl)_2$	0.5	32	59
9	5	CH_2Cl_2	0.5	96	
10	1	CH_2Cl_2	0.5	96	
11	0.2	CH_2Cl_2	24	trace	95

[a] Isolated yield.

sample. Catalyst at 0.2 mol % afforded only trace amounts of product even in CH_2Cl_2 (entry 11). Mercuric acetylide formation is a possible catalyst suicide mechanism but the level of this possible side product was too low to detect.[9]

The reaction of **5** is thought to be initiated by π-complexation of an alkynyl group with $Hg(OTf)_2$ as seen in **8** (Scheme 2). Nucleophilic participation of the carbonyl group

Scheme 2. Proposed Mechanism of $Hg(OTf)_2$-Catalyzed S_N2 Reaction



leads to oxocarbenium cation **9** and this cationic residue acts as the highly efficient leaving group for the S_N2 reaction. Nucleophilic attack of the nitrogen group produces indoline **6** and an enol lactone **10** containing a vinylmercury group. Protonation of **10** by in situ generated TfOH results in a second oxocarbenium cation intermediate **11** that yields γ-methylene-γ-lactone (**2**) along with regenerated catalyst $Hg(OTf)_2$. Finally, $Hg(OTf)_2$ induces isomerization of **2** into more stable enol lactone **7**.[10]

Since the reaction of **5** to **6** is a nucleophilic substitution on the primary carbon center, there is no doubt that it is an

(6) (a) Nishizawa, M.; Skwarczynski, M.; Imagawa, H.; Sugihara, T. *Chem. Lett.* **2002**, 12−13. (b) Nishizawa, M.; Yadav, V. K.; Skwarczynski, M.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 1609−1611. (c) Nishizawa, M.; Takao, H.; Yadav, V. K.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 4563−4565. (d) Imagawa, H.; Kurisaki, T.; Nishizawa, M. *Org. Lett.* **2004**, *6*, 3679−3681. (e) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Org. Lett.* **2005**, *7*, 451−453. (f) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Synlett* **2005**, 703−705. (g) Imagawa, H.; Asai, Y.; Takano, H.; Hamagaki, H.; Nishizawa, M. *Org. Lett.* **2006**, *8*, 447−450. (h) Kurisaki, T.; Naniwa, T.; Yamamoto, H.; Imagawa, H.; Nishizawa, M. *Tetrahedron Lett.* **2006**, *47*, 1871−1874. (i) Yamamoto, H.; Nishiyama, M.; Imagawa, H.; Nishizawa, M. *Tetrahedron Lett.* **2006**, *47*, 8369−8373.

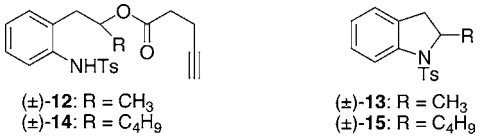
(7) (a) Imagawa, H.; Fujikawa, Y.; Tsuchihiro, A.; Kinoshita, A.; Yoshinaga, T.; Takao, H.; Nishizawa, M. *Synlett* **2006**, 639−641. (b) Imagawa, H.; Kinoshita, A.; Fukuyama, T.; Yamamoto, H.; Nishizawa, M. *Tetrahedron Lett.* **2006**, *47*, 4729−4731.

(8) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525−7546.

(9) Camps, M.; Montheard, J. P.; Benzaid, A. *Bull. Soc. Chim. Fr.* **1989**, 123−129.

(10) Lactonization of **1** with $Hg(OTf)_2$ in CH_3CN results in isomerization to conjugated lactone **7**, whereas, $Hg(OTf)_2$•3TMU gives enol lactone **2** selectively. See ref 7a.

Scheme 3



S_N2 reaction. However, S_N2 reactions can also take place on secondary carbons. Thus, we next examined the secondary alcohol derivatives. Treatment of (±)-**12** with 1 mol % of $Hg(OTf)_2$ in CH_2Cl_2 at 25 °C for 30 min afforded (±)-**13**[11] in only 10% yield leaving 70% unreacted starting material (Scheme 3). However, the reaction in CH_2Cl_2 under reflux conditions for 30 min afforded (±)-**13** in 86% yield. The butyl homologue (±)-**14** was also converted to (±)-**15** under the same conditions in 72% yield.

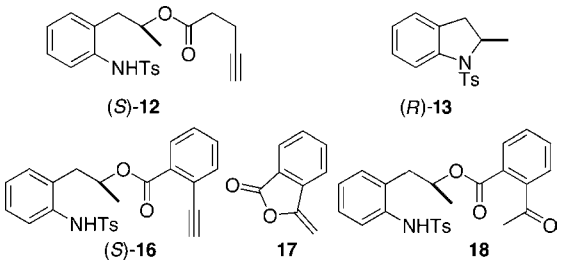
Table 2. $Hg(OTf)_2$-Catalyzed Reaction in CH_2Cl_2 To Give (*R*)-**13**

entry	$Hg(OTf)_2$ (mol %)	temp (°C)	time (h)	yield[a] (%)	% ee
1	1[b]	43	0.5	86	93
2	1[c]	25	3	94	95
3	1[c]	0	24	27	97
4	5[c]	25	3	94	93
5	10[c]	0	2	95	94
6[d]	1[c]	25	2	82	97
7[d]	1[c]	0	3	80	98
8[d]	1[c]	−10	14	66	>99

[a] Isolated yield. [b] CH_3CN solution of $Hg(OTf)_2$ was employed. [c] CH_3CN was completely evacuated. [d] Reaction of (*S*)-**16**.

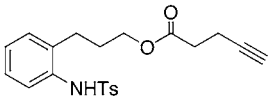
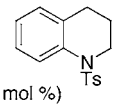
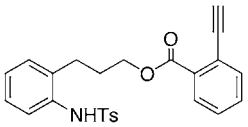
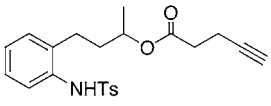
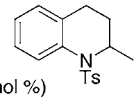
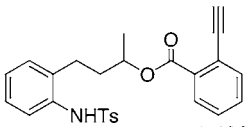
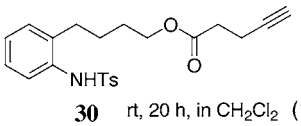
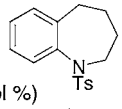
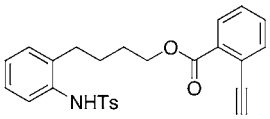
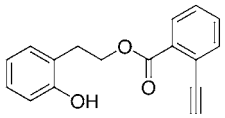
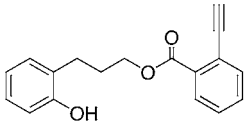
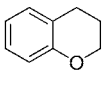
A signature feature of the S_N2 reaction is the stereochemical inversion. Thus, the reaction of optically pure (*S*)-**12**[12] with 1 mol % of $Hg(OTf)_2$ in CH_2Cl_2 at 43 °C for 30 min was examined. The product obtained in 86% yield was shown to be (*R*)-**13** as determined by $[\alpha]_D$ data with 93% ee based on the chiral HPLC analysis (Table 2, entry 1).[13] Then, we found that complete removal of CH_3CN from the reaction

Scheme 4



(11) Liu, X. Y.; Li, C. H.; Che, C. M. *Org. Lett.* **2006**, *8*, 2707−2710.

Table 3. $Hg(OTf)_2$-Catalyzed S_N2 Reaction in CH_2Cl_2

substrate	conditions	$Hg(OTf)_2$ (mol %)	product (% yield)[a]
	rt, 2.5 h, in CH_2Cl_2	1	 25 (91%)
	rt, 2 h, in CH_2Cl_2	1	25 (99%)
	rt, 12 h, in CH_2Cl_2	1	 28 (33%)
	reflux, 2.5 h, in CH_2Cl_2	1	28 (53%)
	rt, 10 h, in CH_2Cl_2	1	28 (69%)
	rt, 20 h, in CH_2Cl_2	1	 31 (5%)
	reflux, 18 h, in CH_2Cl_2	1	31 (5%)
	rt, 12 h, in CH_2Cl_2	1	31 (6%)
	reflux, 17 h, in $(CH_2Cl)_2$	1	31 (36%)
	reflux, 14 h, in $(CH_2Cl)_2$	10	31 (89%)
	rt, 12 h, in $CDCl_3$	1	 34 (29%[b])
	rt, 12 h, in $CDCl_3$	1	 36 (50%[a] 59%[b])

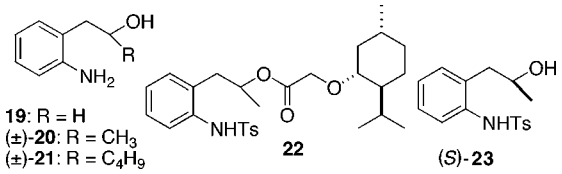
[a] Isolated yield. [b] NMR yield with CH_2Br_2 as an internal standard.

mixture increases the reactivity of $Hg(OTf)_2$, and the reaction of (*S*)-**12** with 1 mol % of $Hg(OTf)_2$ was completed within 3 h even at 25 °C, affording (*R*)-**13** in 94% yield and 95% ee (entry 2). Although the reaction at 0 °C afforded the product in 97% ee, the yield was only 27% after 24 h (entry 3). Increased catalyst loading did not increase the optical purity of product (entries 4 and 5). Finally, we changed the

(12) Absolute structure of (*S*)-*N*-(2-(2-hydroxypropyl)phenyl)-4-methylbenzene sulfonamide [(*S*)-**23**] was established by the Kusumi method by preparing (*R*)- and (*S*)-MTPA derivatives. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

leaving group to 2-ethynylbenzoate and prepared (*S*)-**16** (Scheme 4). Reaction of (*S*)-**16** with 1 mol % of $Hg(OTf)_2$ in CH_2Cl_2 at 25 °C for 2 h afforded (*R*)-**13** in 82% yield with 97% ee (entry 6) along with exomethylene lactone **17**. Furthermore, the same reaction at 0 °C for 3 h also afforded (*R*)-**13** in 80% yield with 98% ee (entry 7), while the reaction at −10 °C for 14 h afforded (*R*)-**13** in 66% yield with >99% ee (entry 8). In the latter case we detected the occurrence of hydrated product **18** in 27% yield. Thus, we obtained the stereochemical inversion with this novel catalytic activated S_N2 reaction.

Scheme 5



4-Pentynoates **5**, (±)-**12**, and (±)-**14** were prepared from corresponding aminoalcohols **19**,[14] (±)-**20**,[15] and (±)-**21**[16] via tosylation followed by esterification (Scheme 5). Optically pure (*S*)-**12** (>99% ee) and (*S*)-**16** were prepared by HPLC separation of diastereomeric menthol derivatives **22**, followed by hydrolysis to (*S*)-**23**[12] and re-esterification with 4-pentynoic acid and 2-ethynylbenzoic acid, respectively.

The applicability of the procedure to the preparation of other ring systems was also examined and the results are summarized in Table 3. Reaction of 4-pentynoate **24**[15] with 1 mol % of $Hg(OTf)_2$ in CH_2Cl_2 at room temperature for 2.5 h afforded tetrahydroquinoline derivative **25** in 91% yield.[17] Alternatively, 2-ethynylbenzoate **26** also provided **25** in 99% yield under similar conditions. 4-Pentynoate **27**, derived from a secondary alcohol,[15] gave methyl homologue **28** in 33% yield after 12 h at room temperature, and 53% yield after 2.5 h at reflux temperature,[17] while 2-ethynylbenzoate **29** afforded **28** in 69% yield even after 10 h at room temperature. Tetrahydrobenzoazepin synthesis by the reaction with 4-pentynoate **30**[15] failed; however, the reaction of 2-ethynylbenzoate **32** with 1 mol % of $Hg(OTf)_2$ at reflux temperature in dichloroethane afforded **31** in 36% yield along with hydrated ketonic product and starting material in 34% and 19% yield, respectively, even though the reaction was carried out under extra dry conditions. A 89% yield of **31** was accomplished by using 10 mol % of catalyst at reflux in dichloroethane for 14 h.[18] Although the procedure is not suitable for benzofuran synthesis from 2-ethynylbenzoate as **33** afforded **34**[19] in only 29% NMR yield along with hydrated ketone formation, synthesis of chroman **36** was achieved in acceptable yield (NMR yield 59%, isolated yield 50%) by using 1 mol % of catalyst in $CDCl_3$.[20]

Thus, we have developed a novel catalytic activation of the leaving group for a S_N2 reaction using 4-pentynoate or 2-ethynylbenzoate as the leaving groups and our original reagent, $Hg(OTf)_2$, as the catalyst, which proceeds with high catalytic turnover under very mild reaction conditions. Although partial epimerization occurred when the leaving group was 4-pentynoate, the problem was lessened by using 2-ethynylbenzoate. The procedure was shown to be applicable for tetrahydroquinoline, benzoazepine, and chroman syntheses, but not for the synthesis of dihydrobenzofuran. We are now working on the application of this process to intermolecular S_N2 reactions.

Acknowledgment. We are grateful to Ms. Kie Masui of this institute for technical assistance. This study was financially supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology of the Japanese Government, and a MEXT.HAITEKU, 2003−2007.

Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701737X

(13) (a) Sakata, T.; Ueshima, Y.; Muro, H.; Maruyama, S.; Tetsuo, M.; Okamoto, K. *Iyakuhin Kenkyu* **1980**, *11*, 388−394. (b) Kuwano, R.; Kashiwabara, M.; Sato, K.; Ito, T.; Kaneda, K.; Ito, Y. *Tetrahedron*: *Asymmetry* **2006**, *17*, 521−535.

(14) Minin, P. L.; Walton, J. C. *J. Org. Chem.* **2003**, *68*, 2960−2963.

(15) Fujita, K.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2002**, *4*, 2691−2694.

(16) Torii, S.; Tanaka, H.; Murakami, Y.; Okamoto, K. *Jpn. Kokai Tokkyo Koho* **1988**, 8.

(17) Fisher, G. H.; Schultz, H. P. *J. Org. Chem.* **1974**, *39*, 635−640.

(18) Cromarty, A.; Proctor, G. R. *Chem. Commun*. **1968**, 842−843.

(19) Pouchert, C. J.; Behnke, J. *The Aldrich Library of ^{13}C and ^{1}H NMR Spectra*, 1st ed.; Aldrich Chemical CO.: Milwaukee, IL, 1993; Vol. 2, p 226-A. Although the NMR signals corresponding to **34** overlapped with those of the authentic sample, isolation of **34** was not successful due to the small quantity of material and its high volatility.

(20) Boyd, D. R.; Sharma, N. D.; Bowers, N. I.; Boyle, R.; Harrison, J. S.; Lee, K.; Bugg, D. H.; Gibson, D. T. *Org. Biomol. Chem.* **2003**, *1*, 1298−1307.

(21) Procopiou, P. A.; Brodie, A. C.; Deal, M. J.; Hayman, D. F.; Smith, G. M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2249−2256.