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# Aldehyde Bis-arylation by Metal Triflates Including Bismuth Triflate Powder

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## Abstract:

**Development of an efficient catalytic reaction promoted by a metal triflate has been emphasized in contemporary synthesis. To evaluate the potential of some metal trflates such as bismuth triflate in our process research, we devised here an expedient protocol for its preparation and characterization. Comparison of its catalytic activity with other well-known metal triflates such as scandium triflate and copper triflate was made in a glyoxylate arylation reaction, which is a useful transformation for the construction of a 1,1-diarylethane skeleton. Furthermore, NMR analysis of $Bi(OTf)_3$ in acetone-$d_6$ revealed the unique nature and reactivity of the triflate, which has not heretofore been disclosed.**

## Introduction

Continuing efforts have been made to attain efficiency and safety (in both the operational and environmental sense) for the conventional aromatic acylation and alkylation processes (Friedel–Crafts reactions). Currently, a catalytic use of metal trifluoromethanesulfonate derivatives in nonhalogenated media is often recommended in these respects.[1] Of special interest is the rare earth triflates [$RE(OTf)_3$], because of their water-tolerance and recyclable nature.[2] It is as yet premature for us to judge whether these new promoters (of large molecular weight) will supplant the classic Lewis acid catalysts (of small molecular weight) in a more demanding substrate. We thus started to experiment with such triflates as $Sc(OTf)_3$, $Cu(OTf)_2$, $Bi(OTf)_3$, and other triflates in our process-oriented research. We disclose herein our preliminary experimentation with such metal triflates, focusing on some beneficial aspects of bismuth triflate.

**Preparation and Characterization of $Bi(OTf)_3$ Powder.** Soon after we started our study on catalytic acylation, Dubac and co-workers announced a surprising catalytic activity of $Bi(OTf)_3$ in a Friedel–Crafts acylation.[3] This prompted us to investigate large-scale preparation of bismuth triflate and its subsequent application in our process research.

On the basis of the Dubac protocol, we devised a simpler preparative protocol as shown below. We selected toluene (instead of the undesirable $CH_2Cl_2$) as the best solvent for preparation and work-up. Protodemetalation of triphenylbismuth with triflic acid was complete within 3 h at room temperature (as opposed to 10 h in $CH_2Cl_2$ as per Dubac) and gave a homogeneous solution, from which a fine powdered $Bi(OTf)_3$ [BIT powder] was obtained after simple evaporation of toluene as shown below. As an extension, bismuth mesylate was obtained in the similar manner.

**NMR Analysis.** Dubac recently reported key spectroscopic information about $Bi(OTf)_3$. Our BIT powder, as prepared above, was identical in $^1H$-, $^{13}C$-, and F NMR with those reported by Dubac in acetone-$d_6$ solution. These analyses precluded the major contamination by the bis-triflate [$PhBi(OTf)_2$] and toluene. Besides key distinctive peaks in $^1H$ and $^{13}C$ NMR, we observed *new peaks gradually appearing during an overnight scan for $^{13}C$ measurement in acetone-$d_6$*. Analysis of these new peaks indicated the formation of acetone aldol and mesityl-d oxide through a catalytic action of $Bi(OTf)_3$. While Dubac did not mention this side reaction, the aldol reaction of deuterated acetone was useful and effective in judging the activity of self-made triflate prior to its use (Scheme 1).

As a preliminary survey, it was interesting to compare the NMR time course of $Bi(OTf)_3$, $Sc(OTf)_3$, and $Cu(OTf)_2$. Just after sampling, only faint peaks of aldol products were observed in the case of BIT solution in $CD_3COCD_3$. Within 12 h, the solution of BIT in $CD_3COCD_3$ turned to black, and peaks of mesytil-d oxide became evident. On the other hand, progress of the aldol reaction was very slow with $Sc(OTf)_3$, and it took 7 days to become the same mixture as BIT mentioned above. In the case of $Cu(OTf)_2$, no aldol reaction was observed even after 1 month standing as $CD_3COCD_3$ solution. We thus observed the difference in Lewis acid activity of some triflates by simple NMR analysis.

**Glyoxylate Bis-arylation.** After the spectroscopic analysis, we conducted some synthetic reactions with metal triflates to evaluate their synthetic potential. Especially, in relation to our process research on some arylpiperazines [OPC-14597 (Aripiprazole)],[4] we investigated a glyoxylate arylation as shown below (Scheme 2).

The reaction of dichloroanisole (DCA) with ethyl glyoxylate polymer (EGP) under the influence of a catalytic metal triflate afforded *para,para*-dimer **1** in good yield after

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(1) For very recent topics, see: (a) Kotsuki, H.; Ohishi, T.; Inoue, M.; Kojima, T. *Synthesis* **1999**, 603–606 and references therein. (b) Matsuo, J.; Odashima, K.; Kobayashi, S. *Synlett* **2000**, 403–405 and references therein.

(2) For reviews, see: (a) Kobayashi, S. *Synlett* **1994**, 689–701. (b) Marshman, R. W. *Aldrichimica Acta* **1995**, *28*, 77–84. (c) Kobayashi, S. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 370–380.

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(4) Oshiro, Y.; Sato, S.; Kurahashi, N.; Tanaka, T.; Kikuchi, T.; Tottori, K.; Uwahodo, Y.; Nishi, T. *J. Med. Chem.* **1998**, *41*, 658–667.

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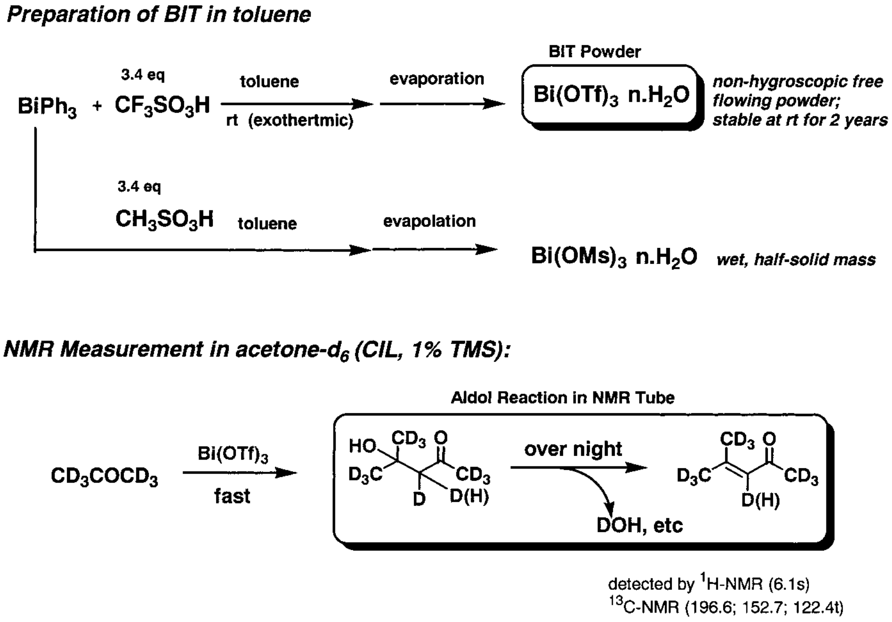
**Scheme 1.** Preparation and NMR measurement of BIT



heating for 2−3 h. Both with $Sc(OTf)_3$ (at 150−170 °C) and $Bi(OTf)_3$ (at 135 °C), the reaction worked well at 40−100 g scale with 0.05−0.1 mol % triflate. These catalysts were easily filtered off from the mixture after dilution with solvents, and could be reused after azeotopic drying with toluene. The symmetric structure of the product (**1**) was easily assigned on the basis of the NMR analysis (COSY and NOESY indicated *para*-substitution as shown). Thus, the OMe group in the substrate was a key functionality for the successful transformation, as well as reliable structural determination. Attempted reactions with some aniline derivatives (2,3-dichloroanilines and 2,3-dichlorophenylpiperazines) gave no coupling products.

Among the other triflates examined, $Hg(OTf)_2$[5] showed exceptional catalytic activity and led to a clean formation of the dimer **1**. The mild reagent $Cu(OTf)_2$ was an alternative safe choice for this conversion, albeit at low yield (∼50%). It should be noted here that $Hg(OTf)_2$ formed a clear reaction mixture, while the other triflates led to an insoluble mixture (suspension), from which catalysts were removed without difficulty. The bismuth mesylate [$Bi(OMs)_3$] prepared above was less effective as $Cu(OTf)_2$. TfOH itself afforded a rather messy mixture under comparable reaction conditions (presumably due to demethylation at high temperatures).

Further experimentation revealed that a similar reaction of *m*-chloroanisole (MCA) gave a more complex mixture, in which a substantial amount of the isomer (*o,p*-dimer) and their hydrolysis product (carboxylic acid) were formed along with the desired product ( ∼30−40% yield after chromatography) as indicated in the scheme. For such reaction, we utilized a convenient catalyst system: $Sc(OTf)_3-MgSO_4-SiO_2$. We observed that less hydrolysis product was formed in the mixture, which resulted in an easy separation of the product. These results indicated $Sc(OTf)_3$ catalyzed both arylation by EGP and subsequent hydrolysis by $H_2O$ formed during the reaction.

We also discovered that $Bi(OTf)_3$ prepared in situ in the reaction flask was a suitable reagent for related reaction with *m*-chlorophenol (MCP) and acetal. MCP was more reactive in this bis-arylation reaction, and some polymerization products or other side-products were formed as a over reaction at phenol OH. Addition of $SiO_2$ and cosolvents such as $CH_2Cl_2$ was particularly useful to prevent polymerization and to form a homogeneous mixture. For the structural assignment, the product **2** obtained from the reaction with MCA was converted to the product **3** obtained from MCP through the sequence shown below (Scheme 2).

Further applications of $Bi(OTf)_3$ in catalytic acylation (chloroacetylation and trichloroacetylation) have also been carried out with substrates related to our process research.[6] Details of this progress will be reported in due course.

In summary, we disclose herein a user-friendly preparation of the $Bi(OTf)_3$ (BIT) powder which was stable and active after ∼2-year storage in the usual flask container. It usually contains about 7% $H_2O$ after long-term storage at room temperature, which was determined by the analysis (Karl-Fisher apparatus) and monitored by NMR in acetone-$d_6$. In the glyoxylate arylation reaction shown above, BIT powder showed comparable activity with $Hg(OTf)_2$ and $Sc(OTf)_3$. Easy preparation in a large quantity (from triphenylbismuth) as well as a stable and recyclable nature demonstrated its superiority to other triflates for contemporary synthesis. Exceptionally low toxicity is another benefit of bismuth salts, which will expand its catalytic and stoichiometric use in medicinal chemistry.

In our NMR analysis of the metal triflates in acetone-$d_6$, we observed an aldol reaction of acetone promoted by the

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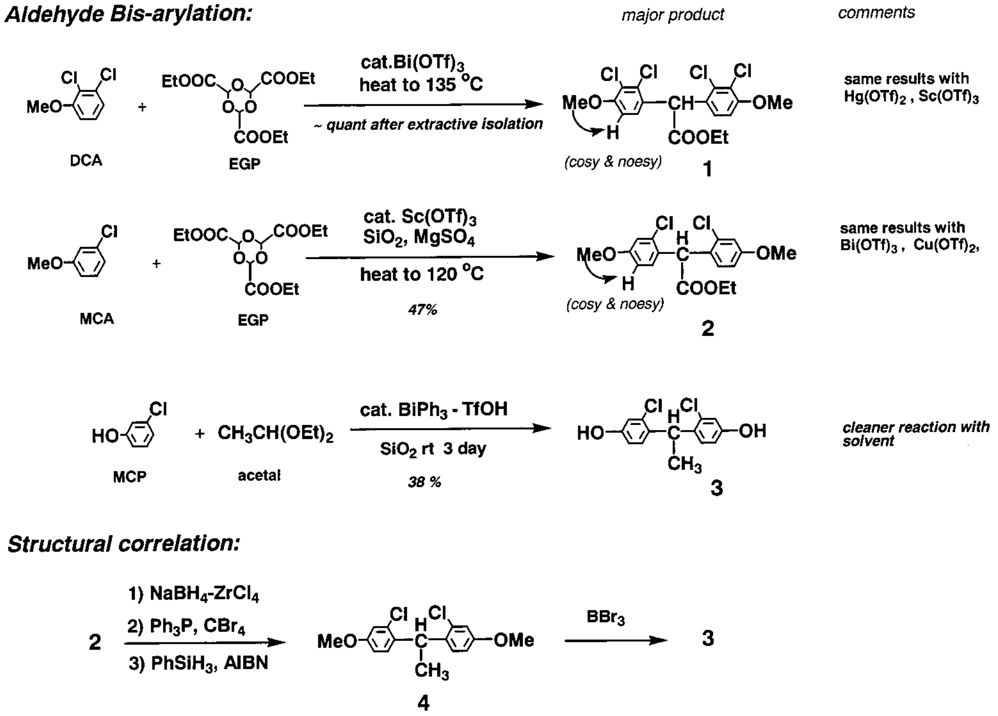
(5) (a) Nishizawa, M.; Morikuni, E.; Asoh, K.; Kan, Y.; Uenoyama, K.; Imagawa, H. *Synlett* **1995**, 169−170. (b) We also prepared a powder of $Hg(OTf)_2$ from the reaction of $HgPh_2$ and triflic acid as described in $Bi(OTf)_3$.

(6) Torisawa, Y.; Nishi, T.; Minamikawa, J. Abstracts of the 120th meeting of Pharmaceutical Society of Japan, Gifu, 2000, p 111.

*Scheme 2.* **Glyoxylate bis-arylation**



triflate to produce mesityl-d oxide. We are now extending this NMR assay to other metal triflates to monitor the reactivity of metal triflates towards solvent acetone. This convenient assay reflects the nature of the reagent (association with water) and its catalytic activity towards simple carbonyls (formation of mesityl oxide).

## Experimental Section

**Materials and Instrumentation.** Chemicals were purchased from commercial firms indicated and used without further purification. TLC analysis was carried out using Merk silica gel 60 $F_{254}$ plate (Art 5715). $^1$H- and $^{13}$C NMR spectra were measured at 300 and 75 MHz, respectively, with tetramethylsilane as the internal standard. NMR solvents ($CDCl_3$, $CD_3COCD_3$) were purchased from Cambridge Isotope Laboratory (CIL). Infrared (IR) spectra were recorded with a Perkin-Elmer 1600 series FTIR apparatus. Mass spectra were recorded with a Shimadzu GCMS-QP1000 spectrometer at 70 eV.

**Preparation of BIT Powder.** A neat solution of $CF_3SO_3H$ (TCI, 25.0 g) was added at room temperature to a stirred solution of $Ph_3Bi$ (Strem, 22.5 g) in toluene (250 mL). After an exothermic process had ceased, the colored mixture was kept stirring for 3 h at room temperature before being concentrated under reduced pressure to form a free-flowing solid mass of $Bi(OTf)_3$ (quant).

**Solvent System.** As indicated above, toluene was found to be the most convenient solvent to obtain a good powder from the reaction mixture by simple evaporation with proper heating. In a reaction using $CH_2Cl_2$, acetonitrile, and DME, the resulting solid mass was gradually changed in color to orange-brown during storage at room temperature.

**NMR Measurement.** $^1$H NMR measurement in acetone-$d_6$ (1% TMS, CIL) indicated the presence of some toluene and attached $H_2O$, and elemental analysis of this sample did not give correct values (Anal. Calcd for $BiC_3F_9S_3$: C, 5.49; H, 0.00. Found: C, 6.32; H, 1.95). Karl-Fisher analysis indicated constant water content at 6.98−7.00%. This BIT powder prepared in our hands was identical with solvent-free material reported by Dubac in $^{13}$C-and F NMR.[3] After $^{13}$C NMR measurement (one overnight, ~12 h), there appeared the clear peaks of mesityl-d oxide: 196.6, 152.7, 122.4t, plus satellites at 67.7, 52.3, 26.70, 17.71. The long-stored material could be further azeotropically dried by toluene under reduced pressure to furnish the sample of constant water content (~7%) as a nonhygroscopic powder.

**Reaction of DCA with EGP. (A) By $Bi(OTf)_3$.** EGP solution (50% in toluene, TCI, 40.0 mL) was first concentrated under reduced pressure to obtain neat EGP (20 g), to which was added DCA (Aldrich, 45 g, 257 mmol), and the whole was heated at around 80 °C to form a clear homogeneous solution. To this was next added $Bi(OTf)_3$ powder (1.0 g) in one portion. The resulting mixture was gradually heated to 110°C ( ~1 h). After monitoring the reaction by TLC, the mixture was further heated at ~135 °C for 1 h. The insoluble reagent precipitated after dilution with $CH_2Cl_2$ at room temperature was recovered through filtration and washing with $CH_2Cl_2$. The filtrate was washed with saturated aqueous $NaHCO_3$ and concentrated to give nearly pure product as orange oil (**1**) (60 g). **1**: $^1$H NMR ($CDCl_3$) $\delta$ 1.28 (3H, t, $J = 4$ Hz), 3.90 (6H, s), 4.25 (2H, q, $J = 4$ Hz), 5.70 (1H, s), 6.82 (2H, d, $J = 8.7$ Hz), 6.94 (2H, d, $J = 8.7$ Hz). $^{13}$C NMR ($CDCl_3$) $\delta$ 171.2; 155.4; 134.0; 128.6; 127.2; 122.3; 109.5; 61.5; 56.2; 52.0; 13.9. MS (EI) *m/z* 436 ($M^+$), 438, 440.

**(B) By $Sc(OTf)_3$.** To a homogeneous mixture of the neat EGP (40.0 g) and DCA (100 g) preheated at around 70 °C was added $Sc(OTf)_3$ (Aldrich, 1.0 g), and the resulting mixture was gradually heated to 150−170 °C. Heating was continued for 1 h to form a dark brown mixture. TLC analysis indicated the complete disappearance of starting material with concomitant formation of the more polar products. The mixture was cooled to room temperature and diluted with $CH_2Cl_2$. The insoluble precipitate was then recovered through filtration and washing with $CH_2Cl_2$. The filtrate was washed with saturated aqueous $NaHCO_3$ and concentrated to give crude product as a brown oil (**1**) (130 g).

**(C) By $Hg(OTf)_2$.** To a homogeneous mixture of the neat EGP (2.5 g) and DCA (5.0 g) preheated at around 70 °C was added $Hg(OTf)_2$ (70 mg), and the resulting mixture was gradually heated to 135 °C. Heating was continued for ∼1 h until TLC analysis indicated the complete disappearance of starting material with concomitant formation of the more polar products. The mixture was cooled to room temperature and diluted with $CH_2Cl_2$. The insoluble precipitate formed after standing was separated by decantation followed by washing with $CH_2Cl_2$. The filtrate was washed with saturated aqueous $NaHCO_3$ and concentrated to give nearly pure product as orange oil (**1**) (5.5 g).

**Reaction of MCA with EGP. (A) By $Sc(OTf)_3$.** Solids of $Sc(OTf)_3$ (500 mg) and $SiO_2-MgSO_4$ (2:1; 5 g) were heated at 130−140 °C for 1 h. To this fine powder was added MCA (TCI, 25.0 g, 175.3 mM) and neat EGP (10.0 g) at around 80 °C. The mixture was then heated 110−120 °C for ∼3 h. TLC then indicated the formation of desired product as a less polar spot. Heating was then ceased, and the mixture was diluted with $CH_2Cl_2$ before the addition of $SiO_2$ (10 g). The solid mass was filtered off and washed with $CH_2Cl_2$. The filtrate was washed with saturated aqueous $NaHCO_3$ and concentrated to give crude products. The mixture was then purified by $SiO_2$ column (AcOEt/*n*-hexane = 1/7) to give two less polar fractions, from which the desired dimer **2** was isolated as a colorless oil (15.2 g, 47.0%). **2**: $^1$H NMR ($CDCl_3$) $\delta$ 1.25 (3H, t, $J = 7$ Hz), 3.77 (6H, s), 4.22 (2H, q, $J = 7$ Hz), 5.64 (1H, s), 6.76 (2H, dd, $J = 8.7$, 2.7 Hz), 6.97 (4H, m). $^{13}$C NMR ($CDCl_3$) $\delta$ 171.9; 159.3; 135.0; 130.1; 127.5; 115.1; 112.8; 61.4; 55.4; 50.1; 14.1. MS (EI) *m*/*z* 368 ($M^+$), 370.

**(B) By $Bi(OTf)_3$.** A solid mass of $Bi(OTf)_3$ (500 mg) with $SiO_2-MgSO_4$ (1:1; 3 g) was heated at 130 °C for 2 h. To this fine powder was added MCA (25.0 g) and neat EGP (10.0 g) at around 80 °C. The mixture was then heated 130 °C for ∼2 h. Heating was ceased, and the mixture was diluted with $CH_2Cl_2$. The solid mass was filtered off and washed with $CH_2Cl_2$. The filtrate was concentrated to give crude yellow products. The mixture was purified by $SiO_2$ column to give two less polar fractions, among which the desired dimer **2** was obtained as a colorless oil (14.5 g, 44.8%).

**Reaction of MCP with Acetal.** To a stirred solution of triphenylbismuth (8.0 g) in $CH_2Cl_2$ (40 mL) was added at room temperature triflic acid (5.0 mL) dropwise under cooling. The resulting mixture was kept stirring at room temperature for 0.5 h, before the addition of $SiO_2$ (50 g) and $CH_2Cl_2$ (40 mL). To this suspension was added MCP (25.0 g) and acetal (25.0 mL) under adequate stirring, and the mixture was kept stirring at room temperature for 3 days. After the completion of the reaction, the mixture was diluted with $CH_2Cl_2$, and the insoluble solids were filtered . Filtrates were concentrated to give crude product as black oil, which was further purified by repeated $SiO_2$ column chromatography to give **3** (10.6 g, 38.5%). **3:** $^1$H NMR ($CDCl_3$) $\delta$ 1.50 (3H, d, $J = 7.1$ Hz), 4.74 (1H, q, $J = 7.1$ Hz), 4.83 (2H, bs, OH), 6.68 (2H, dd, $J = 8.4$, 2.7 Hz), 6.87 (2H, d, $J = 2.7$ Hz), 6.97 (2H, d, $J = 8.4$). $^{13}$C NMR ($CDCl_3$) $\delta$ 154.2; 134.6; 134.3; 128.6; 116.4; 113.8; 36.8; 20.9; 13.9. MS (EI) *m*/*z* 282 ($M^+$), 284.

**Conversion of 2 into the 1,1-Diarylethane (3).** To a stirred solution of the ester **2** (22.8 g, 61 mM) in DME (250 mL) was added $ZrCl_4$ powder (30.0 mM), and to the resulting mixture was added $NaBH_4$ (145.5 mM) at room temperature slowly and carefully. The mixture was stirred at room temperature for ∼1 h, followed by gradually heated to 80 °C for 0.5 h (only gentle reflux). TLC (AcOEt/*n*-hexane = 1/5) now indicated almost all the starting material consumed. After cooling to room temperature, the mixture was carefully quenched by the slow addition of $H_2O$. The precipitated mixture was diluted with $CH_2Cl_2$. After insoluble solid mass was removed by filtration, resulting organic layer was washed with brine. Evaporation of the dried solvent ($MgSO_4$) gave crude product which was further subjected to azeotoropic drying by toluene to give a crude alcohol (19.1 g) suitable for next bromination. **Caution:** do not heat the reduction mixture immediately after the addition of the reagent ($NaBH_4$).

To a stirred solution of the above alcohol (18.0 g, 55 mM) in $CH_2Cl_2$ (200 mL) was added $Ph_3P$ (64 mM) and $CBr_4$ (64 mM) at room temperature. An instantaneous reaction took place, and the resulting mixture was kept stirring for 3 h. TLC indicated no starting material remained. The mixture was concentrated under reduced pressure to give crude product, which was further purified by $SiO_2$ column to give nearly pure bromide (14.0 g).

To a preheated solution of the bromide obtained above (14.0 g, 35.8 mM) in phenylsilane (14.0 g) was added AIBN (150 mg), and the resulting mixture was heated at 110−120 °C for 0.5 h. TLC (AcOEt/*n*-hexane = 1/6) indicated that one-half of the starting material remained unchanged. Further amount of AIBN (150 mg ×2) was added, and the mixture was heated at 130−140 °C for 0.5 h interval. TLC showed almost no starting material. The mixture was subjected to evaporation to give yellow residue, which was further purified by $SiO_2$ column (AcOEt/*n*-hexane = 1/7) to give pure material (**4**) (11.3 g).

To a stirred solution of **4** (3.44 g) in $CH_2Cl_2$ (30 mL) was added at room temperature a $CH_2Cl_2$ solution of $BBr_3$ (30 mL, 1 M solution). The resulting mixture was kept stirring at room temperature overnight until TLC indicated no starting material remained. The mixture was carefully quenched by the addition of $H_2O$ and extracted with $CH_2Cl_2$. The organic layer was washed with $H_2O$ and brine and concentrated after drying. Evaporation of the solvent gave nearly pure material (**3**) as a colorless oil (2.77 g) identical with the product obtained from the reaction on MCP and acetal.

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