Efficient Asymmetric Synthesis of Prostaglandin E_1

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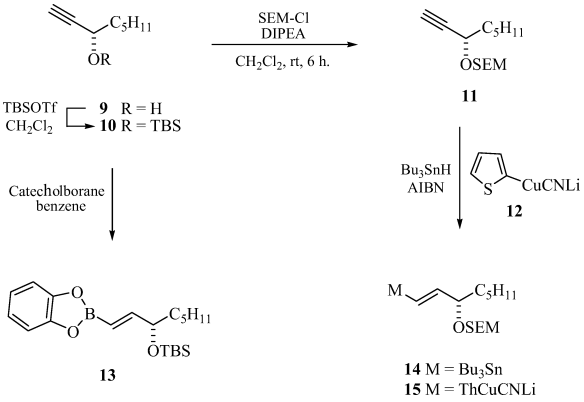
A simple synthesis of prostaglandin E_1 (PGE_1) is described. The key steps are an asymmetric Michael addition to establish the desired (*R*)-configurations at C8 and C12 of the 2-(trimethylsilyl)ethoxymethyl- (SEM) protected PGE_1 and its one-pot deprotection with magnesium bromide in high yield. This method is potentially useful for the preparation of other modified prostaglandins.

Key words: Prostaglandin, Asymmetric Michael Addition, Cuprates, Deprotection

Introduction

Prostaglandin and its analogues have important functions in the animal body and a variety of biological effects [1]. Many naturally occurring prostaglandins as well as many artificial forms have been synthesized by several groups [2]. The major approaches to the synthesis of prostaglandins fall into three categories (Fig. 1). Key steps in the original approach included a Wittig reaction of aldehyde **2** and triphenylphosphane (**3**), followed by a Wittig-Horner reaction to furnish the C13–C14 *E*-olefin partial structure of prostaglandins [3]. Another strategy employed Michael addition reactions of ester **5** and allylic alcohol **6** [4]. In an alternative approach, the Noyori reaction of cyclopentenone **7** with allylic alcohol **6** and *Z*-allylic iodide **8** readily generated prostaglandins, which is the most elegant synthetic method in the area of three component coupling [5].

Since the first isolation of prostaglandins, numerous synthetic methods have been developed [6]. Most of these routes are based on two or three component coupling reactions. Recently, Feringa reported an enantioselective synthesis using a tandem 1,4-addition aldol reaction to a cyclopentene-3,5-dione monoacetal [7]. Florent generated a chiral amino-cyclopentenone moiety *via* [3.3] sigmatropic rearrangement and palladium-catalyzed cross-coupling followed by a ring closing metathesis (RCM) reaction [8].



Scheme 1. Synthesis of key fragments **13** and **15**.

During our studies of asymmetric Michael addition reactions of cyclopentenones, we realized that a more efficient method of preparing prostaglandin E_1 (PGE_1, **1**) and its analogues was needed. Herein, we describe an efficient synthesis of prostaglandin E_1 (**1**) *via* asymmetric Michael addition employing 2-(trimethylsilyl)ethoxymethyl (SEM) protecting groups.

Results and Discussion

Synthesis of fragments **13** and **14** required the development of a method for preparing *tert*-butyldimethylsilyl (TBS) or SEM-protected ethers **10** and **11** in excellent yields (Scheme 1). These were ac-

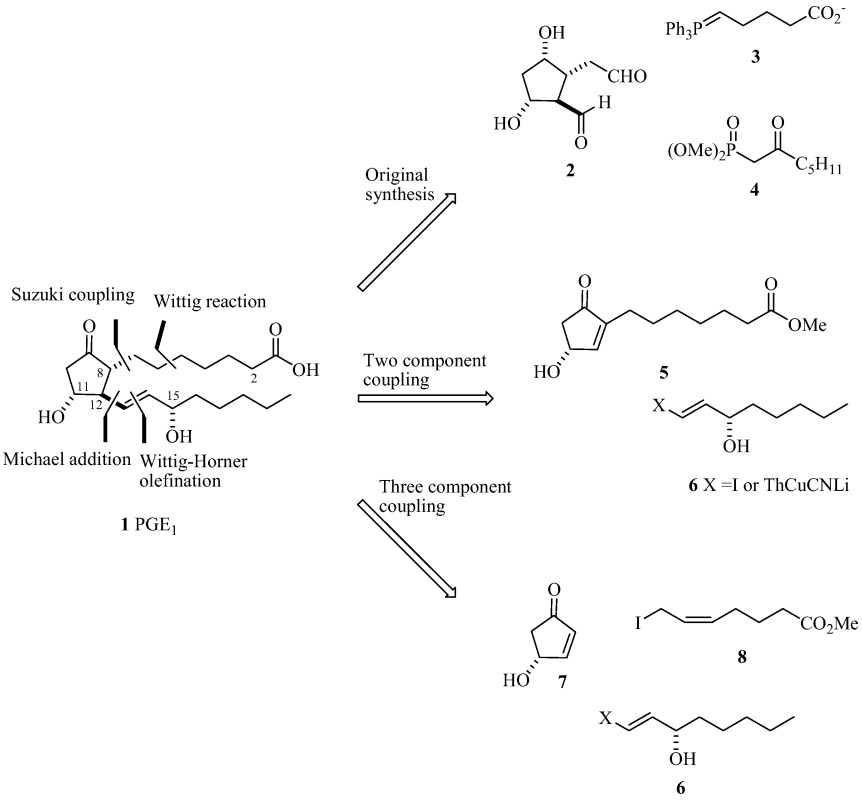
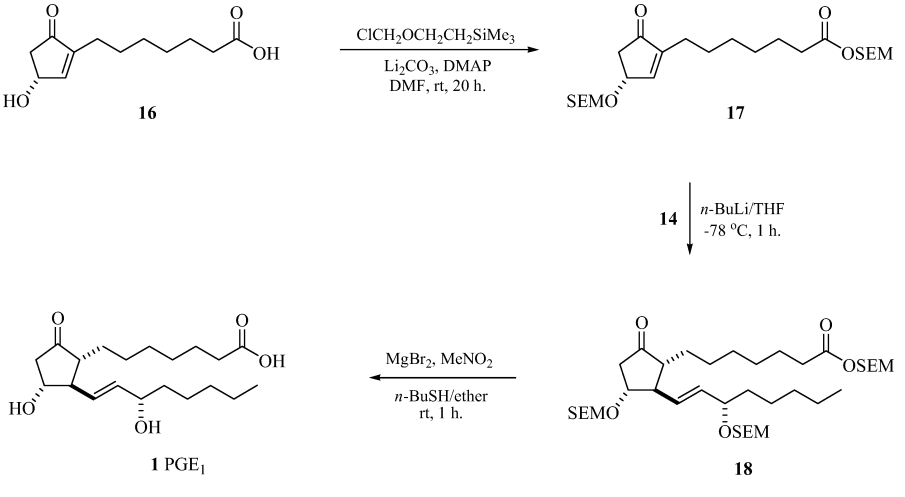


Fig. 1. General synthetic approaches to prostaglandins.



Scheme 2. Synthesis of prostaglandin E_1 (**1**).

complished by subjecting commercially available (*S*)-(–)-1-octyn-3-ol (**9**) to TBS or SEM protection. Fragment **13** was smoothly prepared from TBS-ether **10** which underwent hydroboration with catecholborane in benzene in 80 % yield [9]. *E*-Vinylstannane **14** was obtained from SEM-ether **11** through hydrostannation with tributyltin hydride (Bu_3SnH) in the presence of 2,2′-azo-bis-isobutyronitrile (AIBN) as an initiator in 70 % yield [10]. Bis-protection of the commercially available chiral hydroxyl acid **16** [11] with 2 equiv. of SEM-Cl in the presence of lithium carbonate (Li_2CO_3) and 4-(dimethylamino)pyridine (DMAP)

gave SEM-cyclopentenone **17**. Asymmetric Michael addition of **17** with *E*-vinylstannane **14** [12] in the presence of *n*-BuLi at −78 °C in THF gave fully protected SEM-ester **18** in 67 % yield. However, treatment of **17** with vinylborane **13** was unsatisfactory, and for the most part, the starting material was recovered. Finally, treatment of fully protected SEM-ester **18** with magnesium bromide and nitromethane in the presence of 1-butanethiol [13] led to prostaglandin E_1 (**1**) (Scheme 2), whose spectral and physical data were identical to those reported [14].

In conclusion, the asymmetric synthesis of prostaglandin E_1 (**1**) was accomplished in a three-step process. The use of asymmetric conjugated addition to construct (*R*)-configurations at C8, C12 and an efficient deprotection of fully protected SEM-ester **18** under mild reaction conditions provided an economical and practical method for the preparation of prostaglandins.

Experimental Section

Reactions requiring anhydrous conditions were performed with the usual precautions for rigorous exclusion of air and moisture. Tetrahydrofuran was distilled from sodium benzophenone ketyl prior to use. Thin layer chromatography (TLC) was performed on precoated silica gel G and GP uniplates from Analtech and visualized with 254 nm UV light. Flash chromatography was carried out on silica gel 60 [Scientific Adsorbents Incorporated (SAI), particle size 32 – 63 μm, pore size 60 Å]. ^{1}H NMR, ^{13}C NMR, and 2D NMR spectra were recorded on Bruker DPX 400, 500 instruments at 400 MHz, 500 MHz and 100 MHz, 125 MHz, respectively. The chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane, and *J* values are in Hz. Infrared (IR) spectra were obtained on an ATI Mattson FT/IR spectrometer. Mass spectra were recorded with a Waters Micromass ZQ LC-Mass system and high-resolution mass spectra (HRMS) were measured with a Bruker BioApex FTMS system by direct injection using an electrospray interface (ESI). When necessary, chemicals were purified according to the reported procedures [15].

*(S)-3-(2-Trimethylsilylethoxymethoxy)oct-1-yne (**11**)*

To a stirred solution of (*S*)-(–)-1-octyn-3-ol (**9**, 0.26 g, 2.0 mmol) in dry CH_2Cl_2 (5 mL) was added DIPEA (0.39 g, 3.0 mmol) under argon atmosphere at 0 °C, followed by addition of SEM-Cl (0.4 g, 2.4 mmol). The reaction mixture was stirred at r. t. for 6 h, and quenched with saturated aqueous NH_4Cl solution (2 mL). The organic phase was separated and washed with water (2 mL) and brine (2 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 3 % EtOAc/hexanes) to afford SEM-ether **11** (0.5 g, 98 %) as a colorless oil. R_f = 0.5 (3 % ethyl acetate in hexanes). – $[\alpha]_D^{24}$ = −128.3 (*c* = 1.1, $CHCl_3$). – IR (neat, NaCl): ν = 3312, 2954, 2894, 1647, 1249, 1024, 836 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 500.14 MHz): δ = 4.93 (d, *J* = 6.8 Hz, 1H, OCH_2O), 4.67 (d, *J* = 6.8 Hz, 1H, OCH_2O), 4.33 (t, *J* = 6.4 Hz, 1H, CH), 3.70 (q, *J* = 10.4 Hz, 1H, CH_2), 3.53 (q, *J* = 6.4 Hz, 1H, CH_2), 2.44 (brs, 1H, CH), 1.75 – 1.69 (m, 2H, CH_2), 1.50 – 1.41 (m, 2H, CH_2), 1.34 – 1.26 (m, 4H, 2 × CH_2), 1.00 – 0.92 (m, 2H, CH_2), 0.89 (t, *J* = 6.8 Hz, 3H, CH_3), 0.01 (s, 9H, $SiMe_3$). – ^{13}C NMR ($CDCl_3$, 125.67 MHz): δ = 92.4 (OCH_2O), 82.8 (C), 73.2 (CH), 65.4 (CH), 65.3 (CH_2), 36.0 (CH_2), 31.5 (CH_2), 24.9 (CH_2), 22.6 (CH_2), 18.1 (CH_2), 14.0 (CH_3), −1.4 ($SiMe_3$, 3C). – HRMS: *m/z* = 257.1944 (calcd. 257.1937 for $C_{14}H_{29}O_2Si$, $[M+H]^+$).

*(S)-3-(2-Trimethylsilylethoxymethoxy)-1-tributylstannyl-1-octene (**14**)*

To a stirred solution of SEM-ether **11** (0.51 g, 2.0 mmol), tributyltin hydride (0.88 g, 3.0 mmol) and 2,2′-azo-bis-isobutyronitrile (4 mg, 0.024 mmol) were added under argon atmosphere and kept for 1 h at 120 °C. The reaction mixture was allowed to cool to r. t. The crude product was purified by flash column chromatography (silica gel, 1 % EtOAc/hexanes) to afford *E*-vinylstannane **14** (0.77 g, 70 %) as a pale yellow oil. R_f = 0.4 (1 % ethyl acetate in hexanes): – $[\alpha]_D^{25}$ = −83.0 (*c* = 0.6, $CHCl_3$). – IR (neat, NaCl): ν = 2956, 2873, 1464, 1377, 1249, 1054, 836 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 500.14 MHz) δ = 6.11 (d, *J* = 19.2 Hz, 1H, CH=CH), 5.78 (dd, *J* = 7.2, 18.8 Hz, 1H, CH=CH), 4.68 (dd, *J* = 6.8, 6.8 Hz, 2H, OCH_2O), 4.00 – 3.95 (m, 1H, CH), 3.80 – 3.73 (m, 1H, CH_2), 3.56 – 3.49 (m, 1H, CH_2), 1.66 – 1.55 (m, 2H, CH_2), 1.52 – 1.43 (m, 6H, 3 × CH_2), 1.38 – 1.25 (m, 12H, 6 × CH_2), 1.00 – 0.81 (m, 20H, 4 × CH_3, 4 × CH_2), 0.04 (s, 9H, $SiMe_3$). – ^{13}C NMR ($CDCl_3$, 125.67 MHz): δ = 148.5 (CH=CH), 131.1 (CH=CH), 91.8 (OCH_2O), 79.9 (CH), 65.0 (CH_2), 35.3 (CH_2), 31.8 (CH_2), 29.1 (3 × CH_2, 3C), 27.4 (3 × CH_2, 3C), 25.2 (CH_2), 22.7 (CH_2), 18.1 (CH_2), 14.1 (CH_3), 13.7 (3 × CH_3, 3C), 9.5 (3 × CH_2, 3C), −1.4 ($SiMe_3$, 3C). – HRMS: *m/z* = 549.3158 (calcd. 549.3150 for $C_{26}H_{57}O_2SiSn$, $[M+H]^+$).

*2-Trimethylsilylethoxymethyl-(R)-3-(2-trimethylsilylethoxymethoxy)-5-oxo-1-cyclopentene-1-heptanoate (**17**)*

To a stirred solution of acid **16** (0.23 g, 1.0 mmol) in dry DMF (3 mL) were added DMAP (3 mg, 0.02 mmol) and lithium carbonate (0.16 g, 2.2 mmol) under argon atmosphere at 10 °C, followed by addition of SEM-Cl (0.37 g, 2.2 mmol) at that temperature. The reaction mixture was stirred at r. t. for 20 h. The reaction mixture was diluted with ether (10 mL) and washed with water (5 mL) and

brine (5 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 15 % EtOAc/hexanes) to afford SEM-cyclopentenone **17** (0.15 g, 31 %) as a pale yellow oil. R_f = 0.4 (15 % ethyl acetate in hexanes). – $[\alpha]_D^{25}$ = −4.0 (c = 0.2, $CHCl_3$). – IR (neat, NaCl): ν = 2951, 2898, 1740 (CO), 1715 (COO), 1408, 1249, 1032, 837 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 500.14 MHz): δ = 7.18 (s, 1H, CH=CH), 5.27, (s, 2H, OCH_2O), 4.78 (d, J = 3.2 Hz, 1H, CH), 4.76 (s, 2H, OCH_2O), 3.71 – 3.61 (m, 4H, 4 × OCH_2), 2.76 (dd, J = 6.0, 18.8 Hz, 1H, CH_2), 2.35 (dd, J = 1.6, 17.6 Hz, 1H, CH_2), 3.23 (t, J = 7.6 Hz, 2H, CH_2), 2.18 (t, J = 7.6 Hz, 2H, CH_2), 1.67 – 1.59 (m, 2H CH_2), 1.53 – 1.46 (m, 2H, CH_2), 1.37 – 1.31 (m, 4H, 4 × CH_2), 0.96 (t, J = 8.4 Hz, 4H, 4 × $SiCH_2$), 0.03 (s, 9H, $SiMe_3$), 0.02 (s, 9H, $SiMe_3$). – ^{13}C NMR ($CDCl_3$, 125.67 MHz): δ = 205.9 (CO), 173.3 (COO), 154.4 (CH), 148.3 (C), 94.5 (CH_2), 88.7 (CH_2), 73.6 (CH), 67.8 (CH_2), 65.5 (CH_2), 42.7 (CH_2), 34.3 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 27.2 (CH_2), 24.7 (CH_2), 24.5 (CH_2), 18.1 (CH_2), 18.0 (CH_2), −1.2 ($SiMe_3$, 3C), −1.4 ($SiMe_3$, 3C). – HRMS: m/z = 487.2903 (calcd. 487.2911 for $C_{24}H_{47}O_6Si_2$, $[M+H]^+$).

*Preparation of 2-thienyl(cyano)copper lithium (**12**, 2-ThCuCNLi)*

To a stirred solution of thiophene (1.56 g, 20.4 mmol) in THF (10 mL) n-BuLi (12.5 mL, 20.0 mmol; 1.6 M solution in hexane) was added at −78 °C under argon atmosphere, and stirring was continued at −78 °C for 30 min. The mixture was transferred to a slurry of copper cyanide (1.8 g, 20.0 mmol) in THF (10 mL). The resulting reaction mixture was warmed to −40 °C and diluted with THF (66 mL) to give a clear solution (0.2 M solution in THF), which was stored in a freezer at −22 °C.

*(8R,11R,12R,15S)-11,15-Bis-(2-trimethylsilylethoxymethoxy)-9-oxo-prost-13-en-1-oic acid 2-trimethylsilylethoxymethyl ester (**18**)*

A solution of vinylstannane **14** (0.12 g, 0.22 mmol) in dry THF (0.5 mL) was treated with n-BuLi (0.15 mL, 0.22 mmol; 1.6 M solution in hexane) at −78 °C under argon atmosphere. The mixture was stirred at −78 °C for 30 min, and a solution of ThCuCNLi (1.4 mL, 0.28 mmol; 0.2 M solution in THF) in THF (0.5 mL) was added. The reaction mixture was stirred at that temperature for 30 min, and a solution of SEM-cyclopentenone **17** (0.1 g, 0.2 mmol) in THF (1 mL) was added. The resulting mixture was stirred at −78 °C for 30 min, and quenched with 10 % aqueous NH_4OH solution (2 mL) and saturated aqueous NH_4Cl solution (3 mL). The mixture was warmed to r. t., diluted with ether (10 mL) and washed with brine (5 mL). The organic layer was separated, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20 % ether/hexanes) to afford fully protected SEM ester **18** (0.1 g, 67 %) as a pale yellow oil. R_f = 0.3 (20 % ether in hexanes). – $[\alpha]_D^{25}$ = +30.7 (c = 1.2, $CHCl_3$). – IR (neat, NaCl): ν = 2951, 1740 (CO), 1716 (COO), 1463, 1249, 1105, 1031, 836 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 500.14 MHz): δ = 6.96 (dd, J = 5.0, 3.8 Hz, 1H, CH=CH), 6.80 (dd, J = 0.8, 3.4 Hz, 1H, CH=CH), 5.29 (s, 2H, OCH_2O), 5.28 (s, 2H, OCH_2O), 4.80 (d, J = 2.4 Hz, 2H, OCH_2O), 4.74 (d, J = 7.2 Hz, 1H, CH), 3.74 – 3.67 (m, 6H, 3 × CH_2), 3.66 – 3.60 (m, 1H, CH), 2.81 (ddd, J = 6.8, 6.4, 6.0 Hz, 2H, CH_2, CH), 2.40 – 2.28 (m, 4H, CH_2, CH), 2.03 (t, J = 11.5 Hz, 2H, CH_2), 1.67 – 1.59 (m, 4H, 2 × CH_2), 1.56 – 1.47 (m, 4H, 2 × CH_2), 1.40 – 1.28 (m, 8H, 4 × CH_2), 1.01 – 0.93 (m, 9H, 3 × CH_2, CH_3), 0.05 (s, 3H, $SiMe_3$), 0.04 (s, 6H, $SiMe_3$), 0.04 (s, 9H, $SiMe_3$), 0.03 (s, 9H, $SiMe_3$). – ^{13}C NMR ($CDCl_3$, 125.67 MHz): δ = 206.0 (CO), 173.5 (COO), 154.5 (CH=CH), 148.6 (CH=CH), 94.7 (CH_2), 93.7 (CH_2), 89.0 (CH_2), 84.9 (CH), 78.7 (CH), 73.7 (CH), 68.0 (CH_2), 65.8 (CH_2), 65.4 (CH_2), 51.6 (CH), 42.9 (CH_2), 34.5 (2 × CH_2, 2C), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 27.7 (CH_2), 27.5 (CH_2), 26.2 (CH_2), 24.9 (CH_2), 24.7 (CH_2), 18.3 (CH_2), 18.2 (2 × CH_2, 2C), −1.2 (3 × $SiMe_3$, 9C). – HRMS: m/z = 745.4932 (calcd. 745.4926 for $C_{38}H_{76}O_8Si_3$, $[M+H]^+$).

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[1] P. W. Collins, S. W. Djuric, *Chem. Rev.* **1993**, *93*, 1533 – 1564.

[2] C. J. Sih, P. Price, R. Sood, R. G. Salomon, G. Peruzzotti, M. Casey, *J. Am. Chem. Soc.* **1972**, *94*, 3642 – 3644; F. Sato, H. Tsujiyama, N. Ono, T. Yoshino, S. Okamuko, *Tetrahedron Lett.* **1990**, *31*, 4481 – 4484; O. W. Gooding, C. C. Beard, G. F. Cooper, D. Y. Jackson, *J. Org. Chem.* **1993**, *58*, 3681 – 3686.

[3] E. J. Corey, N. M. Weinshenker, T. K. Schaaf, W. Huber, *J. Am. Chem. Soc.* **1969**, *91*, 5675 – 5677.

[4] F. S. Alvarez, D. Wren, A. Prince, *J. Am. Chem. Soc.* **1972**, *94*, 7823 – 7827.

[5] R. Noyori, M. Suzuki, A. Yangisawa, *J. Am. Chem. Soc.* **1988**, *110*, 4718 – 4726.

[6] L. V. Hijfte, M. Kolb, *Tetrahedron* **1992**, *48*, 6393 – 6402; C. R. Johnson, M. P. Braun, *J. Am. Chem. Soc.* **1993**, *115*, 11014 – 11015.

[7] L. A. Arnold, R. Naasz, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2001**, *123*, 5841 – 5842.

[8] E. Roulland, C. Monneret, J. C. Florent, *J. Org. Chem.* **2002**, *67*, 4399 – 4406.
[9] N. Miyaura, K. Yamada, H. Suginome, A. Suzuki, *J. Am. Chem. Soc.* **1985**, *107*, 972 – 980; C. F. Lane, *Tetrahedron* **1976**, *32*, 981 – 990.
[10] K. C. Nicolaou, J. Y. Ramphal, Y. Abe, *Synthesis* **1989**, 898 – 901.
[11] Compound **16** was provided by Pharma. Tech. International Inc., New Jersey (USA).
[12] B. H. Lipshutz, *Synthesis* **1987**, 325 – 341; B. H. Lipshutz, M. Koerner, D. A. Parker, *Tetrahedron Lett.* **1987**, *28*, 945 – 948.
[13] J. C. Jung, R. Kache, K. K. Vines, Y. S. Zheng, P. Bijoy, M. Valluri, M. A. Avery, *J. Org. Chem.* **2004**, *69*, 9269 – 9284.
[14] A. Rodriguez, M. Nomen, B. W. Spur, J. J. Godfroid, *Eur. J. Org. Chem.* **1999**, *10*, 2655 – 2662.
[15] D. D. Perrin, L. F. Armarego, D. R. Perrin, *Purification of Laboratory Chemicals*, 2^{nd} ed, Pergamon Press, New York, (USA) **1980**.