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A model study of epothilone synthesis: an alternative synthetic approach to the C1–C7 fragment

GOJKO LALIĆ[#], DANICA GALONIĆ[#], RADOMIR MATOVIĆ[#] AND RADOMIR N. SAIČIĆ[*#]

Faculty of Chemistry, University of Belgrade, Studentski trg 16, P.O. Box 158, YU-11000 Belgrade and Institute of Chemistry, Technology and Metallurgy-Center for Chemistry, Njegoševa 12, YU-11001 Belgrade, Yugoslavia

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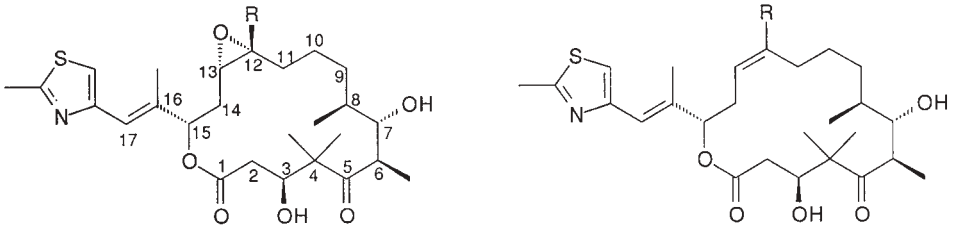
In this model study an alternative synthetic approach to the C1–C7 fragment of epothilones was investigated. Starting from 4,4-dimethylcyclopentenone, a 7 step reaction sequence afforded the key intermediate **7** in 27 % overall yield. Surprisingly, the attempted deprotection of latent functionalities in **7** failed, indicating the incompatibility of the ethoxyethyl protective group with the reaction conditions employed.

Keywords: epothilones, epoxides, enol ethers, alkylations, Lewis acids.

INTRODUCTION

Epothilones are a class of compounds isolated from the myxobacterium *Sorangium cellulosum*,[1] which exibit potent cytotoxic properties against a variety of cell lines (Scheme 1).[2] Owing to the taxol-like mechanism of the antimitotic activity, better water solubility compared to taxol and high potency against taxol-resistant cancer cell lines, epothilones have emerged as extremely promising anti-tumor agents, and have attracted a rarely seen interest of synthetic chemists. Several total syntheses have been



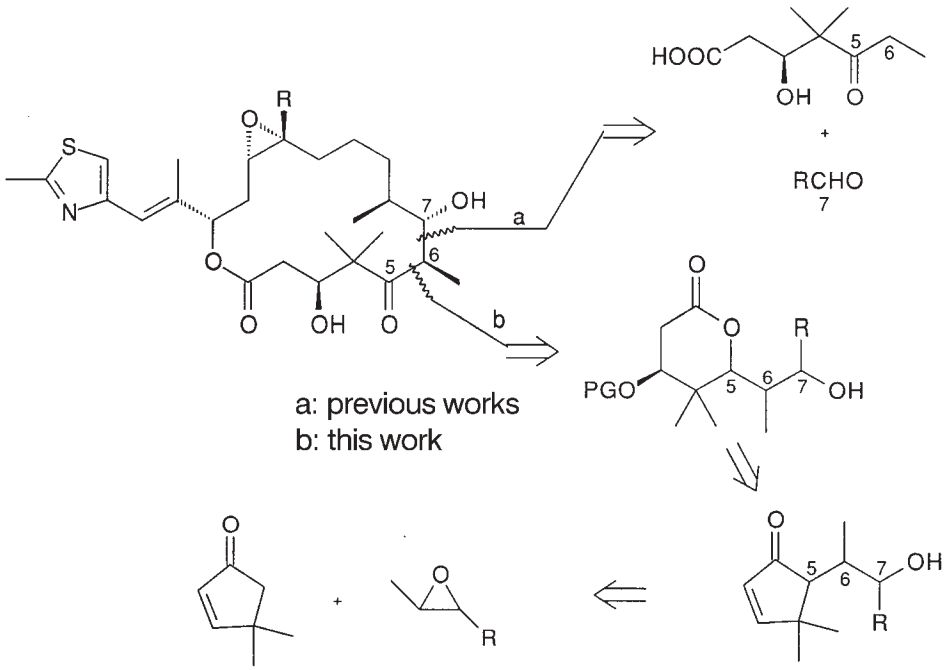
Scheme 1.

* E-mail address: rsaicic@chem.bg.ac.yu

Serbian Chemical Society active member.

reported, as well as numerous studies directed toward the development of efficient, versatile synthesis of multigram quantities of these compounds, for both clinical trials and SAR studies.[3]

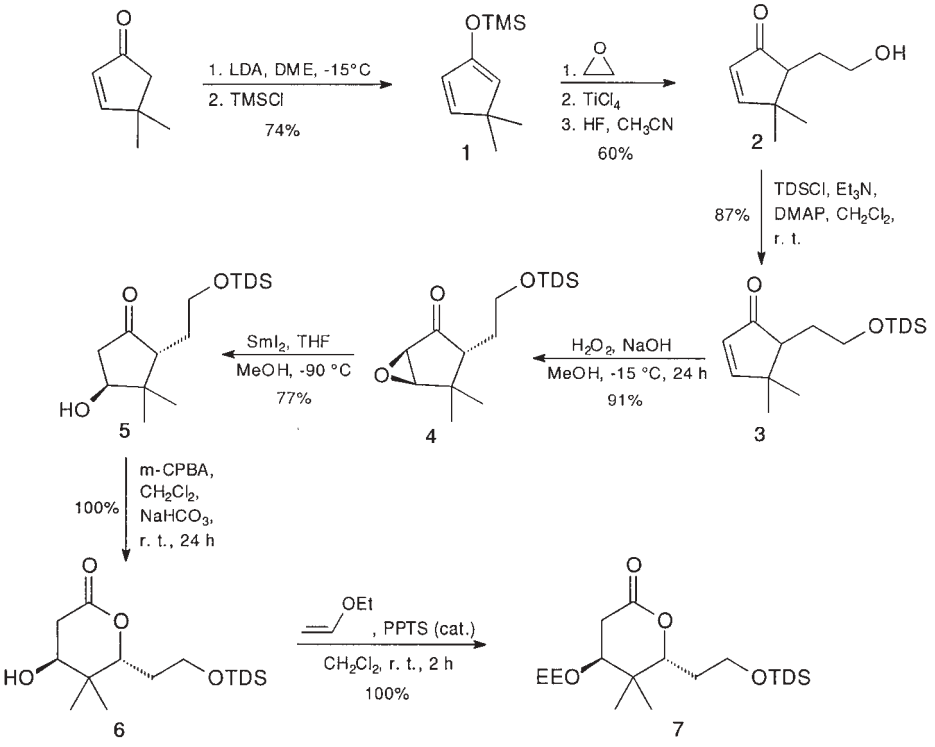
It is interesting to note that all the retrosynthetic analyses, reported so far, share one common feature: the C5–C7 fragment being recognized as an aldol retron, the formation of the C6–C7 bond has been invariably committed to directed aldol technology (Scheme 2, retrosynthetic dissection a). Notwithstanding the efficiency of such an approach, we considered an alternative retrosynthetic pathway, based on the dissection of the C5–C6 bond, as delineated in Scheme 2 (retrosynthetic dissection b). This transformation relies on the enolate-epoxide alkylation transform, which corresponds to a new reaction recently discovered in our laboratory – the alkylation of silyl enol ethers with epoxides under Mukaiyama conditions.[4] The envisioned synthetic approach would enable a convergent access to the C1–C12 epothilone fragment, *via* the coupling of 4,4-dimethylcyclopentenone (as a latent C1–C5 substructure) and an unsaturated epoxide (C6–C12 fragment).



Scheme 2.

Before embarking on a total synthesis of a fully functionalized epothilone molecule, we decided to test the feasibility of this new strategy in the synthesis of 6-demethyl C1–C7 derivative **9** as a model compound. The course of the synthesis is represented in Scheme 3. The readily available 4,4-dimethylcyclopentenone[5] was converted into the corresponding trimethylsilyl enol ether **1** under previously described conditions (74 %).[6] The titanium tetrachloride catalyzed reaction of **1** with ethylene oxide afforded the

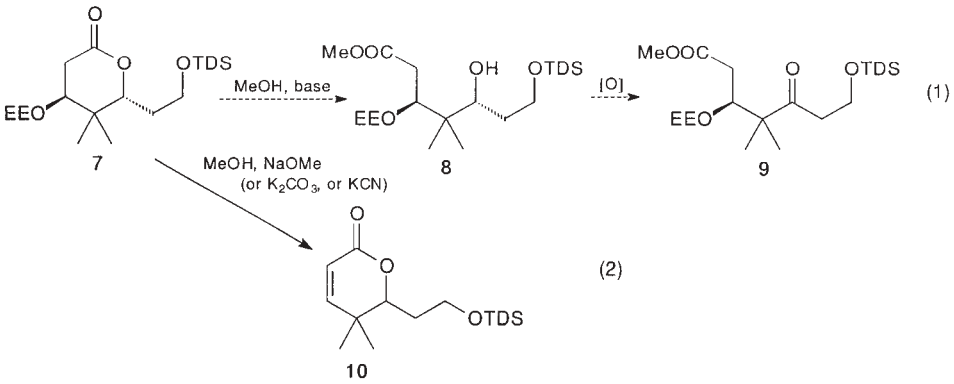
desired alkylated product **2** (60 %),[4] which was further protected as thexyldimethylsilyl (TDS) ether **3** (87 %).[7] The attempted introduction of a 3-hydroxy substituent *via* a base catalyzed hetero-Michael addition failed; therefore, this transformation was accomplished using a two step sequence, *i.e.*: epoxidation/reductive opening of the oxirane ring. Treatment of **3** with basic, aqueous hydrogen peroxide furnished the epoxyketone **4** (91 %).[8] The reaction proceeded with complete stereoselectivity, as a single isomer was obtained; its structure was not determined, but was tentatively assigned as *trans*, according to literature precedents.[9] Samarium(II) iodide mediated reductive opening of epoxyketone **4** proceeded without event, providing the β-hydroxyketone **5** in 77 % yield.[10] Baeyer-Villiger oxidation of **5** proceeded with complete regioselectivity, furnishing the desired hydroxylactone **6** in quantitative yield. In this way both the introduction of the C5-oxygen functionality and "deprotection" of the C1-carboxylate were performed in a single synthetic operation. Hydroxylactone **6** was subsequently protected as the ethoxyethyl (OEE) derivative **7** (100 %).[11] Thus, starting from 4,4-dimethylcyclopentenone, the key intermediate **7** was obtained in 7 steps, and in 27 % overall yield (without optimization).



Scheme 3.

With the crucial lactone **7** in hand, there remained only two, apparently simple, steps to successfully complete the synthesis of model compound **9**: methanolysis of the lactone and the oxidation of 5-hydroxy substituent to a carbonyl group (Scheme 4, Eq.

1). However, at this point we met with unexpected difficulties. Upon treatment with basic methanol (MeONa, K_2CO_3, KCN were used as catalysts), lactone **7** underwent elimination of the OEE-group, affording the unsaturated lactone **10** instead of the desired hydroxyester **8** (Eq. 2). This was quite surprising as, to the best of our knowledge, no literature precedents exist pointing to the proclivity of the OEE group toward elimination. On the other hand, an attempt to diminish the nucleofugacity of the protective group also failed, as hydroxylactone **6** was inert toward thexyldimethylsilyl chloride under a variety of conditions (TDSCl, Et_3N, DMAP, CH_2Cl_2; TDSCl, imidazole, DMF; TDSCl, $AgNO_3$, Pyr, THF),[12] and decomposed in the presence of thexyldimethylsilyl triflate.[13]



Scheme 4.

The problems encountered with the deprotection of lactone **7** thwarted the successful accomplishment of the synthesis. However, by the efficient synthesis of **6** we believe to have shown that the described chemistry offers a potentially useful approach to the synthesis of epothilones. The unwanted, base catalyzed elimination in the penultimate step will probably be surmounted by a judicious choice of the protective group. The stereoselectivity of the epoxidation step (*e.g.,* **3** → **4**) is noteworthy: although the relative stereochemistry of stereocenters at C3 and C5 in **4** is irrelevant (given the anticipated installation of a carbonyl functionality at C5 in the latter stage of the synthesis), the chirality transfer from C5 to C3 during epoxidation could be of interest as a possible means of controlling the absolute configuration of the C3-substituent, provided that the alkylation of **1** with epoxyde is performed with an asymmetric induction.

EXPERIMENTAL

General remarks

All chromatographic separations were performed on Silica, 10-18, 60A, ICN Biomedicals. Standard techniques were used for the purification of reagents and solvents. The NMR spectra were recorded on a Varian Gemini 200, ^{1}H-NMR at 200 MHz, ^{13}C-NMR at 50 MHz, for samples in deuterated chloroform. Chemical shifts are expressed in ppm using tetramethylsilane as internal standard, coupling constants (*J*) are in Hz. The IR spectra were recorded on a Perkin-Elmer 457 grating

FT instrument, and are expressed in cm^{-1}. The mass spectra were obtained on a Finnigan ITDS 700 instrument. Petroleum-ether refers to the fraction with distillation range 70–90 ºC.

*5,5-Dimethyl-2-trimethylsilyloxy-1,3-cyclopentadiene (**1**)*

n-Butyllithium (1.6 M solution in hexane; 7.14 mL; 11 mmol) was added dropwise to a cold (–15 ºC) solution of diisopropylamine (1.55 mL; 11.07 mmol) in 1,2-dimethoxyethane (20 mL), with stirring, under an argon atmosphere. After 15 min, a solution of 4,4-dimethylcyclopentenone (1.22 mL; 10 mmol) was added dropwise within 5 min. The reaction mixture was stirred for 15 min at the same temperature, after which time chlorotrimethylsilane (2.42 mL; 19 mmol) was added in one portion. The reaction mixture was allowed to reach room temperature, and then stirred for further 2 hours. The solvent was evaporated under reduced pressure, pentane (15 mL) was added, the mixture was filtered through a sintered glass funnel, then evaporated again under reduced pressure. Distillation under reduced pressure afforded 1.34 g (74 %) of the title compound **1**, as a colourless liquid, E_2 = 40 ºC (E_6 = 45–7 ºC).

^{1}H-NMR: 6.08 (*dd*, J_1 = 5.4, J_2 = 2.4, 1H); 5.83 (*dd*, J_1 = 5.4, J_2 = 1.7, 1H); 5.03 (*t*, J = 2.05, 1H); 1.08 (*s*, 6H); 0.14 (s, 9H).

*4,4-Dimethyl-5-(2-hydroxyethyl)-cyclopent-2-en-1-one (**2**)*

To a cold (–78 ºC) solution of **1** (860 mg; 3.97 mmol) and ethylene oxide (396 μL; 7.94 mmol) in CH_2Cl_2 (58 mL), $TiCl_4$ (11.91 mL of 1 M solution; 11.91 mmol) was added dropwise, with stirring under an argon atmosphere. After completion of addition, the reaction mixture was allowed to reach – 60 ºC. After 2 h the initially dark-red coloured reaction mixture turned faint-pink, when the reaction was quenched with H_2O (20 mL). The CH_2Cl_2 layer was separated, the aqueous layer extracted twice with CH_2Cl_2, and the combined organic extract evaporated under reduced pressure. The crude reaction product was dissolved in CH_3CN (30 mL), and stirred for 2 h at room temperature with a few drops of dilute aqueous HF. The reaction mixture was partitioned between water and CH_2Cl_2, the organic extract was washed with dilute aqueous $NaHCO_3$ and water, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. Purification by dry-flash chromatography (eluent: petroleum-ether:acetone = 9:1) afforded 370 mg (60 %) of the title compound **2** as a colourless oil.

IR_{film}: 3403 (br), 2960, 2871, 1697, 1590, 1046; ^{1}H-NMR: 7.52 (1H, *d*, J = 5.6, *H*C:CHC:O), 6.05 (1H, *d*, J = 5.6, :C*H*C:O), 3.92–3.76 (3H, *m*, CH_2OH), 2.26–2.19 (1H, *m*, *H*CC:O), 1.81–1.74 (2H, *m*, CH_2CH$_2$OH), 1.26 (3H, *s*, CH_3), 1.07 (3H, *s*, CH_3); ^{13}C-NMR: 212.8 (C), 173.5 (CH), 129.9 (CH), 62.4 (CH_2), 56.8 (CH), 44.8 (C), 28.6 (CH_2), 26.9 (CH_3), 24.7 (CH_3); $MS/CI_{isobutane}$: 155 $(M+H)^+$, 137 $(M+H-H_2O)^+$; HRMS (EI):M^+, found 154.0997. $C_9H_{14}O_2$ requires 154.0994.

*5-(2-Thexyldimethylsilyloxyethyl)-4,4-dimethylcyclopentenone (**3**)*

A solution of **2** (413.1 mg; 2.7 mmol), triethylamine (540.4 μL; 3.9 mmol), TDSCl (578.2 μL; 2.9 mmol) and DMAP (65.5 mg; 0.5 mmol) in dichloromethane (8 mL) was stirred over night at room temperature. As the reaction was not complete, an excess of TDSCl (173.5 μL; 0.9 mmol) and triethylamine (162.0 μL) was added. After 6 h stirring at r. t. additional triethylamine (1.15 mL; 8.3 mmol) was added, and the reaction was complete after 3 h. The reaction mixture was diluted with ether (30 mL), washed successively with saturated aqueous $NaHCO_3$, 1 M aqueous HCl, and finally with aqueous $NaHCO_3$. The organic extract was dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to afford 686.3 mg (87 %) of the title compound **3** as a light yellow oil.

IR_{film}: 2961, 2868, 1713, 1466, 1253, 1094, 832; ^{1}H-NMR: 7.41 (*d*, J = 5.8, 1H); 6.01 (*d*, J = 6.0, 1H); 3.82 (*t*, J =6.4, 3H); 2.23 (*t*, J = 6.8, 1H); 1.91 (*m*, 1H); 1.62 (*m*, 1H); 1.24 (*s*, 3H); 1.05 (*s*, 3H); 0.89 (*s*, 3H); 0.86 (*s*, 3H); 0.84 (*s*, 6H); 0.10 (*s*, 6H); ^{13}C-NMR: 211.55; 172.31; 130.01; 61.17; 53.10; 44.35; 34.14; 29.16; 27.43; 25.03; 24.52; 20.29; 18.48; –3.48; $MS/CI_{isobutane}$: 298 $(M+2H)^+$.

trans-*4,4-Dimethyl-5-(2-thexyldimethylsilyloxyethyl)-2,3-epoxycyclopentanone (**4**)*

Sodium hydroxide (180.4 μL of 6 M aqueous solution; 1.08 mmol) was added with stirring to a cold (–15 ºC) solution of **3** (581.6 mg; 2.17 mmol) in a mixture of methanol (3.8 mL) and THF (2.2 mL). To the resulting solution, 25 % hydrogen peroxide (1.98 mL) was added dropwise, with stirring. The reaction mixture was allowed to reach 0 ºC, and then stirred over night at that temperature. The mixture was diluted with dichloromethane, washed with aqueous NH_4Cl, dried over anhydrous Na_2SO_4, filtered and

evaporated under reduced pressure. Purification by dry-flash chromatography (eluent: petroleum-ether: acetone = 975:25) afforded 458.9 mg (91 %) of the title compound **4** as a colourless oil.

IR_{film}: 2956, 2870, 1747, 1098, 850, 834, 778; ^{1}H-NMR: 3.67 (*m*, 2H); 3.51 (*d*, *J* = 2.8, 1H); 3.33 (*d*, *J* = 2.8, 1H); 2.35 (*dd*, J_1 = 6.8, J_2 = 4.3, 1H); 1.61 (*m*, 2H); 1.25 (*s*, 3H); 0.89 (*s*, 3H); 0.85 (*s*, 3H); 0.82 (*s*, 3H); 0.07 (*s*, 3H); 0.06 (*s*, 3H); ^{13}C-NMR: 212.16; 64.17; 60.91; 54.63; 45.42; 37.98; 34.10; 26.20; 24.95; 23.01; 20.31; 20.22; 18.43; –3.56; –3.62; $MS/CI_{isobutane}$: 313 $(M+H)^+$.

trans-*3,3-Dimethyl-2-(2-thexyldimethylsilyloxyethyl)-4-hydroxycyclopentanone (**5**)*

Samarium powder (407.3 mg; 2.68 mmol) was transferred to a flask under an argon atmosphere. THF (3.2 mL) was added, followed by a solution of diiodomethane (205.4 μL; 1.88 mmol) in THF (3.2 mL), and the reaction mixture was stirred for 2.5 h at ambient temperature under an argon atmosphere. The blue solution of SmI_2 was cooled to –90 ºC, and a solution of **4** (434.6 mg; 1.38 mmol) in a solvent mixture THF (3.2 mL)/MeOH (1.6 mL) was added (the deep blue colour of the reaction mixture immediately turned green). After 5 min the reaction was quenched by the addition of a saturated aqueous K_2CO_3 and the reaction mixture was allowed to reach room temperature with stirring. The mixture was diluted with ether (40 mL), the aqueous layer was extracted with ether (4 × 20 mL). The combined organic extract was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. Purification by dry-flash chromatography (eluent: petroleum-ether:acetone = 9:1) afforded 335.8 mg (77 %) of the title compound **5** as a pale yellow oil.

IR_{film}: 3444, 2957, 1734, 1097, 829; ^{1}H-NMR: 3.98 (*d*, *J* = 5.2, 1H); 3.75 (*m*, 2H); 2.56 (*d*, *J* = 5.4, 1H); 2.47 (*d*, *J* = 2.4, 1H); 2.26 (*d*, *J* = 19.2, 1H); 1.61 (*m*, 3H); 1.17 (*s*, 3H); 0.84 (*m*, 15H); 0.08 (2 × *s*, 6H); ^{13}C-NMR: 219.53; 75.55; 73.36; 61.21; 51.02; 44.98; 43.36; 34.05; 27.39; 24.96; 21.72; 21.59; 20.22; 18.40; –3.51; –3.52; $MS/CI_{isobutane}$: 315 $(M+H)^+$.

trans-*3-Hydroxy-4,4-dimethyl-5-(2-thexyldimethylsilyloxyethyl)-pentanolactone (**6**)*

To a solution of **5** (54.1 mg; 0.17 mmol) in dichloromethane (1.4 mL), $NaHCO_3$ (51.6 mg; 0.61 mmol) was added, followed by 85 % *m*-CPBA (44.4 mg; 0.22 mmol) and the reaction mixture was stirred at room temperature for 3.5 h. Dichloromethane (8 mL) was added and the resulting solution was washed successively with 10 % aqueous Na_2SO_3 and saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to afford 55.7 mg (98 %) of the title compound **6** as white crystals.

^{1}H-NMR: 4.69 (*dd*, J_1 = 8.4, J_2 = 4.0, 1H); 3.76 (*m*, 3H); 2.83 (*dd*, J_1 = 18.7, J_2 = 4.7, 1H); 2.58 (*dd*, J_1 = 18.6, J_2 = 2.6, 1H); 1.71 (*m*, 3H); 1.04 (*s*, 3H); 0.93 (*s*, 3H); 0.90 (*s*, 3H); 0.86 (*s*, 3H); 0.84 (*s*, 6H); 0.10 (2 × *s*, 6H); ^{13}C-NMR: 170.62; 79.00; 72.51; 58.93; 36.56; 35.96; 34.13; 32.70; 25.00; 21.90; 20.27; 18.74; 18.45; –3.52.

И З В О Д

МОДЕЛ СТУДИЈА У СИНТЕЗИ ЕПОТИЛОНА: АЛТЕРНАТИВНИ ПРИСТУП СИНТЕЗИ C1–C7 ФРАГМЕНТА

ГОЈКО ЛАЛИЋ, ДАНИЦА ГАЛОНИЋ, РАДОМИР МАТОВИЋ и РАДОМИР Н. САИЧИЋ

Хемијски факултет, Универзитет у Београду, Студентски трг 16, п. пр. 158, 11000 Београд и ИХТМ – Центар за хемију, Његошева 12, 11001 Београд

У оквиру модел студије испитиван је алтернативни синтетички приступ C1–C7 фрагменту молекула епотилона. Полазећи од 4,4-диметилциклопентенона, кључни интермедијер **7** добијен је у седам фаза, у укупном приносу од 27 %. Депротекцију латентних фунционалних група у молекулу **7** није било могуће извршити, због изненађујуће лабилности етоксиетил заштитне групе у базним реакционим условима.

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