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THE FIRST AND SIMPLE TOTAL SYNTHESIS OF CAPPARILOSIDE A[1]

Masanori Somei* and Fumio Yamada
Faculty of Pharmaceutical Sciences, Kanazawa University,
13-1 Takara-machi, Kanazawa 920-0934, Japan

Abstract — A lithium hydroxide promoted simple glycosylation of 4-hydroxyindole-3-acetonitrile with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide was developed. Utilizing the method, the first and five steps total synthesis of cappariloside A was achieved from indole-3-carbaldehyde in 41% overall yield.

Calis and co-workers[2] isolated capparilosides A (**1**, Scheme 1) and B (**2**) from mature fruits of *Capparis spinosa*, used in folk medicine in Turkey as a diuretic, antihypertensive, etc., and determined them to be indole-3-acetonitrile-4-*O*-β-glucopyranoside and -4-*O*-β-(6'-*O*-β-glucopyranosyl)glucopyranoside, respectively, based on spectral and chemical evidences. Their unique structures and the interest in elucidating their structure-activity relationship prompted us to devise a simple synthetic method for them. The present paper reports on the first total synthesis of **1** in five steps from indole-3-carbaldehyde (**3**).

We have already established two steps synthetic method[3] for supplying 4-benzyloxyindole-3-acetonitrile (**4**) as a readily available building block in 64% overall yield from **3** by developing new reactions.[3] Accordingly, utilizing **4** as a starting material, debenzylation was carried out by catalytic hydrogenation over 10% Pd/C to provide 4-hydroxyindole-3-acetonitrile (**5**)[4] in 82% yield.

In the next glycosylation[5] step, we selected 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[6] (**6**) as a convenient glycosylating reagent and examined its reaction with **5**. Under the reaction conditions using $Bu_4N^+HSO_4^-$ in aq. NaOH–$CHCl_3$ reported by Dess and co-workers,[7] the attempted glycosylation did not take place. After unsuccessful trials with various bases, we have newly found that LiOH is the reagent of choice. In order to facilitate separation and purification of the products, after LiOH promoted reaction of **5** with **6** in DMF, the reaction mixture was acetylated with Ac_2O and pyridine resulting in the formation of the desired compounds, 1-acetyl- (**7**) and/or 4-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyloxy)indole-3-acetonitrile (**8**). Typical results are summarized in Table 1.

In the Entry 1, **5** reacted with **6** (2.2 mol eq) in the presence of LiOH (2.2 mol eq) in DMF, followed by acetylation, to afford **7**, **8**, 4-acetoxyindole-3-acetonitrile (**9**), and 4-acetoxy-1-acetylindole-3-acetonitrile (**10**) in 18, 2, 55, and 6% yields, respectively. The change in the ratio of **6** to LiOH from 1:1 to 1:1.7 (Entry 2), increased the yield of **8** to 8% together with the decrease in that of **7**. Further change in the ratio to 1:2 brought about additional increase in **8** and decrease in **7** (Entry 3). Keeping the ratio to 1:2, when relative quantities of **6** and LiOH to **5** were raised to 5 and 10 mol eq., respectively, dramatical improvement was observed culminating in the formation of **8** and **10** in 53 and 23% yields, respectively,

Scheme 1

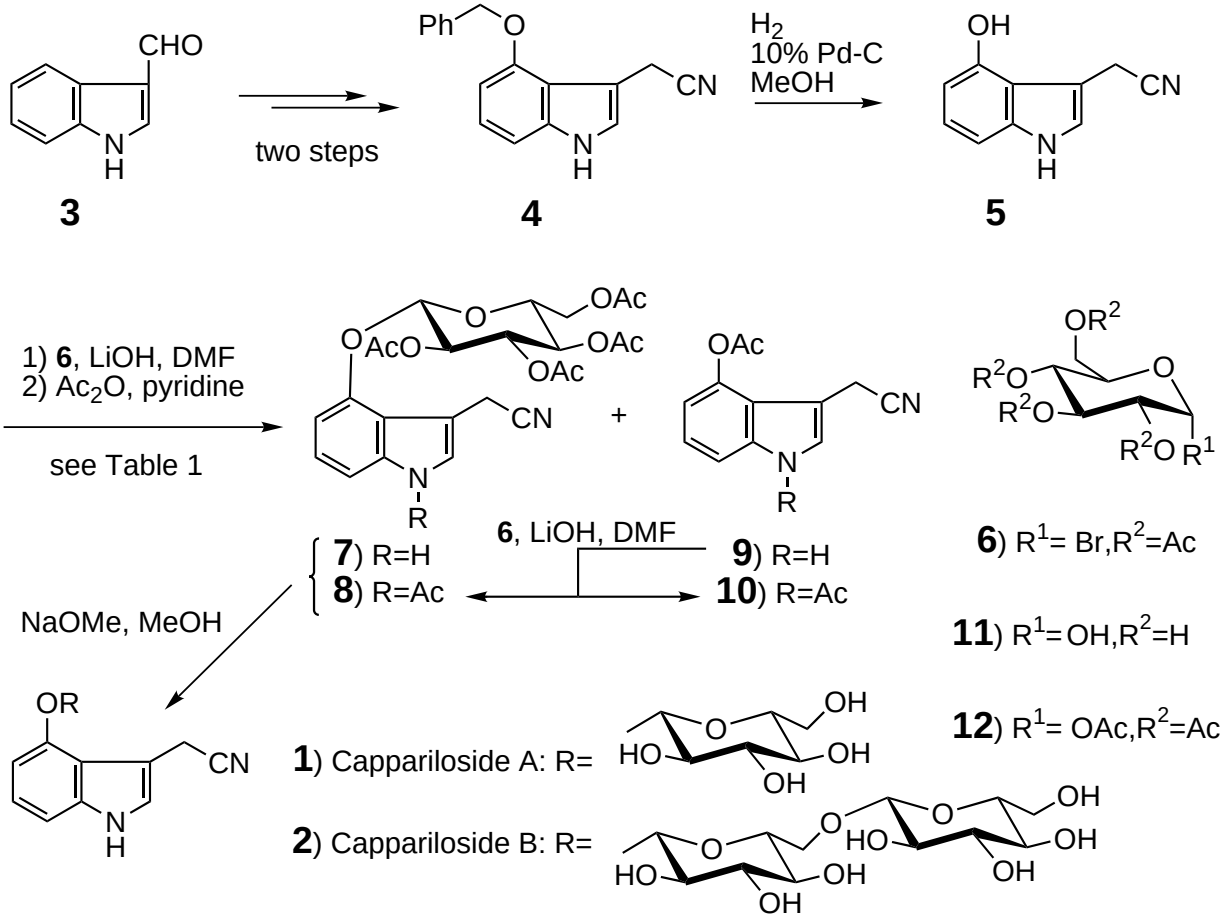

Table 1. Reaction of 4-Hydroxyindole-3-acetonitrile (**5**) with 2,3,4,6-tetra-*O*-Acetyl-α-D-glucopyranosyl Bromide (**6**), followed by Acetylation with Ac_2O and Pyridine

Entry	Reaction Conditions			Yield (%) of			
	6 (mol eq)	LiOH (mol eq)	Time (h)	**7**	**8**	**9**	**10**
1	2.2	2.2	1.5	18	2	55	6
2	1.5	2.6	2	15	8	54	8
3	1.5	3.1	2	12	11	44	10
4	5.3	10.0	2	0	53	0	23
5 *	5.3	10.0	2	79	0	3	0

* The lithium salt of **5** was preformed. See the experimental section.

without a trace amount of formations of **7** and **9** (Entry 4). Similarly, the reaction of **9** with **6** (5 mol eq) and LiOH (10 mol eq) in DMF, followed by treatment with Ac_2O and pyridine, afforded **8** and **10** in 55 and 17% yields, respectively. Finally, we found that the preformed lithium salt of **5**, prepared simply by mixing **5** with LiOH in MeOH followed by evaporation of the solvent, reacted successfully with **6**. Subsequent acetylaion resulted in the formation of **7** (instead of **8**) in 79% yield as shown in the Entry 5.

In another attempts to attain the desired glycosylation, both direct heating of **5** with α-D-glucose (**11**) and the condensation of **5** with α-D-glucose pentaacetate (**12**) in the presence of $ZnCl_2$ in AcOH,[8] were examined under various reaction conditions *in vain*.

Hydrolysis of **7** and **8** using NaOMe in anhydrous MeOH[9] proceeded smoothly to give capparilosides A (**1**) in 98 and 98% yields, respectively. The UV, IR, ^{1}H- and ^{13}C-NMR spectra of synthetic **1**, and its behavior on TLC were identical with those of natural **1**.[2] Although capparilosides A is reported to be amorphous solid, our synthetic one is colorless prisms melting at 235—237°C (decomp). This is the reason why the value of specific rotation of our synthetic **1** is larger than that of natural product.

In conclusion, we have achieved the first total synthesis of capparilosides A (**1**) in five steps from **3** in 41% overall yield with a 67% originality rate.[10] Application of the present simple glycosylation method to other substrates such as phenol and acidic compounds is in progress.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a Shimadzu IR-420 spectrophotometer, and ^{1}H- and ^{13}C-NMR spectra with a JEOL GSX-500 spectrometer with tetramethylsilane as an internal standard. MS were recorded on JEOL SX-102A and JMS-GCmate spectrometers. Column chromatography was performed on silica gel (SiO_2, 100—200 mesh, from Kanto Chemical Co. Inc.) throughout the present study.

4-Hydroxyindole-3-acetonitrile (5) from 4-Benzyloxyindole-3-acetonitrile (4) — A solution of **4** (103.8 mg, 0.396 mmol) in MeOH (10 mL) was hydrogenated at rt and 1 atm over 10% Pd/C (43.6 mg) for 0.5 h. After evaporation of the solvent under reduced pressure, the residue was column-chromatographed on SiO_2 with $CHCl_3$–MeOH (98:2, v/v) as an eluent to give **5** (55.5 mg, 82%). **5**: mp 182—184°C (colorless prisms, recrystallized from AcOEt–hexane). IR (KBr): 3470 (NH or OH), 3280 (NH or OH), 2270 (CN) cm^{-1}. ^{1}H-NMR (CD_3OD) δ: 4.08 (2H, d, *J*=1.2 Hz), 6.35 (1H, dd, *J*=7.6, 0.7 Hz), 6.83 (1H, dd, *J*=8.3, 0.7 Hz), 6.89 (1H, dd, *J*=8.3, 7.6 Hz), 7.05 (1H, br t, *J*=1.2 Hz). MS *m/z*: 172 (M^+). *Anal.* Calcd for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27. Found: C, 69.73; H, 4.67; N, 16.24.

1-Acetyl- (8) and 4-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranosyloxy)indole-3-acetonitrile (7) from 5 — [Entry 1] LiOH (16.4 mg, 0.685 mmol) was added to a solution of **5** (38.3 mg, 0.223 mmol) in DMF (2 mL) and the mixture was stirred at rt for 10 min. To this dark purple solution was added **6** (140.7 mg, 0.342 mmol) and the whole was stirred at rt for 2 h. After addition of AcOH (0.05 mL), the solvent was evaporated under reduced pressure. To the residue were added pyridine (2 mL) and Ac_2O (1 mL), and the mixture was stirred at rt for 21 h. After evaporation of the solvent under reduced pressure, AcOEt was added to the residue. The organic layer was washed with saturated $NaHCO_3$, then

with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a brown oil, which was column-chromatographed on SiO_2 successively with $CHCl_3$–hexane (7:3, v/v) and $CHCl_3$ as eluents to give 4-acetoxy-1-acetylindole-3-acetonitrile (**10**) (8.2 mg, 6%), 4-acetoxyindole-3-acetonitrile (**9**) (70.0 mg, 55%), **8** (7.5 mg, 2%), and **7** (52.3 mg, 18%) in the order of elution. **7**: mp 197—198 ℃ (colorless needles, recrystallized from MeOH). $[\alpha]_D^{26}$ –24.0° (*c*=0.15, $CHCl_3$). IR (KBr): 3380 (NH), 2260 (CN), 1749 (CO), 1724 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.04 (3H, s), 2.058 (3H, s), 2.059 (3H, s), 2.08 (3H, s), 3.92 (1H, ddd, *J*=10.0, 5.4, 2.4 Hz), 3.96 (1H, dd, *J*=19.0, 1.2 Hz), 4.02 (1H, dd, *J*=19.0, 1.2 Hz), 4.15 (1H, dd, *J*=12.3, 2.4 Hz), 4.29 (1H, dd, *J*=12.3, 5.4 Hz), 5.21 (1H, dd, *J*=10.0, 9.3 Hz), 5.33—5.43 (3H, m), 6.61 (1H, dd, *J*=7.0, 1.7 Hz), 7.09 (1H, dd, *J*=8.3, 1.7 Hz), 7.11 (1H, dd, *J*=8.3, 7.0 Hz), 7.19 (1H, dt, *J*=2.4, 1.2 Hz), 8.19 (1H, br s, NH). MS *m/z*: 502 (M^+).*Anal.* Calcd for $C_{24}H_{26}N_2O_{10}$: C, 57.37 ; H,5.22 ; N, 5.58. Found : C,57.32 ; H,5.22 ; N,5.49.**8** : mp 213 - 214°C (colorless needles, recrystallized from MeOH). $[\alpha]_D^{26}$ –37.7° (*c*=0.13, $CHCl_3$). IR (KBr): 2260 (CN), 1743 (CO), 1728 (CO), 1705 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.03 (3H, s), 2.058 (3H, s), 2.062 (3H, s), 2.09 (3H, s), 2.64 (3H, s), 3.90 (1H, ddd, *J*=10.0, 5.4, 2.4 Hz), 3.92 (1H, dd, *J*=19.7, 1.5 Hz), 4.02 (1H, dd, *J*=19.7, 1.5 Hz), 4.13 (1H, dd, *J*=12.5, 2.4 Hz), 4.29 (1H, dd, *J*=12.5, 5.4 Hz), 5.16—5. 24 (1H, m), 5.32—5.39 (3H, m), 6.81 (1H, d, *J*=7.8 Hz), 7.30 (1H, dd, *J*=8.3, 7.8 Hz), 7.42 (1H, br t, *J*=1.5 Hz), 8.19 (1H, *J*=8.3 Hz). MS *m/z*: 544 (M^+). *Anal*. Calcd for $C_{26}H_{28}N_2O_{11}\cdot 1/4H_2O$: C, 56.88; H, 5.23; N, 5.10. Found: C, 56.80; H, 5.20; N, 5.06. **9**: mp 135—136 ℃ (colorless prisms, recrystallized from AcOEt–hexane). IR (KBr): 3400 (NH), 2250 (CN), 1759 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 3.87 (2H, d, *J*=1.2 Hz), 6.93 (1H, dd, *J*=7.6, 1.0 Hz), 7.15 (1H, dt, *J*=2.4, 1.2 Hz), 7.19 (1H, dd, *J*=8.3, 7.6 Hz), 7.23 (1H, dd, *J*=8.3, 1.0 Hz), 8.27 (1H, br s, NH). MS *m/z*: 214 (M^+). *Anal*. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.35; H, 4.76; N, 12.99. **10**: mp 173—174°C (colorless prisms, recrystallized from AcOEt). IR (KBr): 2260 (CN), 1752 (CO), 1697 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s), 2.64 (3H, s), 3.86 (2H, d, *J*=1.2 Hz), 7.12 (1H, dd, *J*=8.1, 0.7 Hz), 7.38 (1H, dd, *J*=8.3, 8.1 Hz), 7.44 (1H, br t, *J*=1.2 Hz), 8.34 (1H, br d, *J*=8.3 Hz). MS *m/z*: 256 (M^+). *Anal*. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.59; H, 4.67; N, 10.91.

[Entry 2] In the same procedure as described in the Entry 1, LiOH (59.3 mg, 2.48 mmol), **5** (166.7 mg, 0.969 mmol), DMF (6 mL), and **6** (611.1 mg, 1.48 mmol) were used and the reaction time was 2 h. And then, AcOH (0.5 mL), pyridine (4 mL), and Ac_2O (2 mL) were used. Reaction time for acetylation was 3 h. After the same work-up and separation as described in Entry 1, **7** (71.2 mg, 15%), **8** (41.3 mg, 8%), **9** (111.7 mg, 54%), and **10** (19.7 mg, 8%) were obtained.

[Entry 3] In the same procedure as described in the Entry 1, LiOH (31.2 mg, 1.30 mmol), **5** (102.0 mg, 0.593 mmol), DMF (5 mL), and **6** (545.0 mg, 1.32 mmol) were used and the reaction time was 1.5 h. And then, AcOH (0.5 mL), pyridine (5 mL), and Ac_2O (2.5 mL) were used. Reaction time for acetylation was 50 h. After the same work-up and separation as described in Entry 1, **7** (13.4 mg, 12%), 8 (13.1 mg, 11%), **9** (21.0 mg, 44%), and **10** (5.9 mg, 10%) were obtained.

[Entry 4] In the same procedure as described in the Entry 1, LiOH (70.1 mg, 2.93 mmol), **5** (50.2 mg, 0.292 mmol), DMF (5 mL), and **6** (633.9 mg, 1.54 mmol) were used and the reaction time was 1 h. And

then, AcOH (1 mL), pyridine (6 mL), and Ac_2O (3 mL) were used. Reaction time for acetylation was 3 h. After the same work-up as described in Entry 1, the residue was column-chromatographed on SiO_2 with AcOEt–hexane (1:3, v/v) to give **10** (17.3 mg, 23%) and **8** (83.3 mg, 53%) in the order of elution.

[Entry 5] LiOH (66.1 mg, 2.76 mmol) was added to a solution of **5** (46.7 mg, 0.272 mmol) in MeOH (5 mL) and the mixture was stirred at rt for 5 min under Ar atmosphere. After evaporation of the solvent under reduced pressure, a solution of **6** (560.4 mg, 1.36 mmol) in DMF (5 mL) was added to the residue and the whole was stirred at rt for 2 h. After addition of AcOH (1 mL), the solvent was evaporated under reduced pressure. To the residue were added pyridine (6 mL) and Ac_2O (3 mL), and the mixture was stirred at rt for 3 h. After evaporation of the solvent under reduced pressure, AcOEt was added and the organic layer was washed with saturated $NaHCO_3$, and brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a brown oil, which was column-chromatographed on SiO_2 successively with AcOEt–hexane (1:2, v/v) and AcOEt–hexane (1:1, v/v) to give **9** (1.6 mg, 3%) and **7** (107.8 mg, 79%) in the order of elution.

1-Acetyl-4-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyloxy)indole-3-acetonitrile (8) from 9 — LiOH (78.7 mg, 3.29 mmol) was added to a solution of **9** (68.9 mg, 0.322 mmol) in DMF (5 mL) and the mixture was stirred at rt for 1 h under Ar atmosphere. To this dark purple solution was added **6** (667.8 mg, 1.62 mmol) and the whole was stirred at rt for 2 h. After addition of AcOH (1 mL), the solvent was evaporated under reduced pressure. To the residue were added pyridine (6 mL) and Ac_2O (3 mL), and the mixture was stirred at rt for 14 h. After evaporation of the solvent, AcOEt was added to the residue and the whole was washed with saturated $NaHCO_3$, and brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a brown oil, which was column-chromatographed on SiO_2 with AcOEt–hexane (1:3, v/v) to give **10** (13.6 mg, 17%) and **8** (95.6 mg, 55%) in the order of elution.

Cappariloside A (1) from 7 — A solution of NaOMe in MeOH [prepared with Na (122.0 mg, 5.30 mmol) and anhydrous MeOH (3 mL)] was added to a suspension of **7** (29.0 mg, 0.058 mmol) in anhydrous MeOH (1 mL) at 0 ℃ and the mixture was stirred at rt for 2 h. After the pH of the reaction mixture was adjusted to 6—7 with AcOH (0.3 mL), the whole was evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with AcOEt–MeOH (95:5, v/v) to give **1** (19.0 mg, 98%). **1**: mp 235—237 ℃ (decomp, colorless prisms, recrystallized from MeOH–AcOEt, natural product[2] is reported to be amorphous). $[\alpha]_D^{26}$ –78.5° (*c*=0.15, MeOH) [lit.,[2] $[\alpha]_D^{20}$ –58.8° (*c*=0.4, MeOH)]. IR (KBr): 3500, 3350, 2250 (CN), 1625, 1586, 1502, 1348, 1245, 1169, 1077 cm^{-1}. ^1H - NMR(500MHz, DMSO-d_6) δ: 3.21 (1H, dt, *J*=5.4, 9.2 Hz, collapsed to d, *J*=9.2 Hz on addition of D_2O), 3.27—3.41 [3H, m, collapsed to 3.32 (1H, t, *J*=8.9 Hz), 3.34—3.40 (1H, m), and 3.39 (1H, dd, *J*=9.0, 7.8 Hz) on addition of D_2O], 3.50 (1H, quin, *J*=6.0 Hz, collapsed to dd, *J*=11.7, 5.9 Hz on addition of D_2O), 3.73 (1H, ddd, *J*=11.7, 5.3, 2.0 Hz, collapsed to dd, *J*=11.7, 2.0 Hz on addition of D_2O), 4.14 (1H, dd, *J*=18.6, 0.5 Hz), 4.20 (1H, dd, *J*=18.6, 1.0 Hz), 4.56 (1H, t, *J*=5.7 Hz, OH, disappeared on addition of D_2O), 4.89 (1H, d, *J*=7.6 Hz), 5.00 (1H, d, *J*=5.4 Hz, OH, disappeared on addition of D_2O), 5.08 (1H, d, *J*=4.9 Hz, OH, disappeared on addition of D_2O), 5.28 (1H, d, *J*=5.6 Hz, OH, disappeared on addition of D_2O), 6.69 (1H, dd, *J*=7.1, 1.2 Hz), 6.99 (1H, dd, *J*=8.1, 7.1 Hz), 7.02 (1H, dd, *J*=8.1, 1.2 Hz), 7.20 (1H, br d, *J*=2.4 Hz, collapsed to s on addition of D_2O), 11.06 (1H,

br s, NH, disappeared on addition of D_2O). ^{13}C-NMR (DMSO-d_6) δ: 14.8, 60.6, 69.6, 73.3, 76.4, 76.8, 101.1, 103.3, 103.6, 106.0, 116.5, 120.2, 122.5, 122.7, 137.7, 151.7. FAB-MS *m/z*: (positive) 357 $[M+Na]^+$, (negative) 333 $[M-H]^-$.*Anal*.Calcd for $C_{16}H_{18}N_2O_6$:C,57.48;H,5.43;N,8.38. Found: C,57.26;H,5.48;N,8.14.

Cappariloside A (1) from 8 — A solution of NaOMe in MeOH [prepared with Na (114.8 mg, 4.99 mmol) and anhydrous MeOH (3 mL)] was added to a suspension of **8** (28.9 mg, 0.052 mmol) in anhydrous MeOH (1 mL) at 0 ℃ and the mixture was stirred at rt for 4 h. After the reaction mixture was adjusted to pH 6—7 with AcOH (0.3 mL), the whole was evaporated under reduced pressure to leave a solid, which was column-chromatographed on SiO_2 with AcOEt–MeOH (95:5, v/v) to give **1** (17.1 mg, 98%). The IR, ^{1}H- and ^{13}C-NMR spectra, and its behavior on tlc are identical with those of **1** from **7**.

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