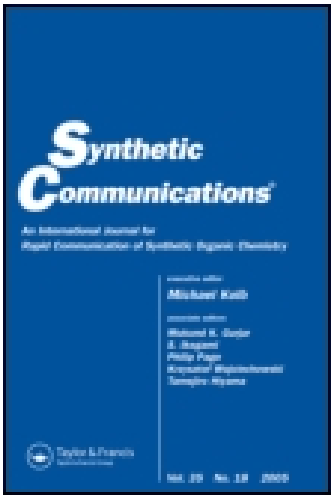

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Synthesis of the Potassium Channel Opener (3S,4R)-3,4-Dihydro-4-(2,3-dihydro-2-methyl-3-o

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Synthesis of the Potassium Channel Opener (3*S*,4*R*)-3,4-Dihydro-4-(2,3-dihydro-2-methyl-3-oxo-pyridazin-6-Yl)oxy-3-hydroxy-6-(3-hydroxyphenyl)sulphonyl-2,2,3-trimethyl-2H-benzo[b]pyran

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Abstract: The preparation of the potassium channel opener (3*S*,4*R*)-3,4-dihydro-4-(2,3-dihydro-2-methyl-3-oxo-pyridazin-6-yl)oxy-3-hydroxy-6-(3-hydroxyphenyl)sulphonyl-2,2,3-trimethyl-2H-benzo[b]pyran (**1**) as a single enantiomer is reported. Considerable improvements have been implemented with respect to the original synthesis that allow for the preparation of multigram quantities of the final target compound. The optimized synthesis consists of a six-step linear sequence whose key step is an asymmetric epoxidation protocol through the use of Jacobsen's (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride catalyst.

Keywords: asymmetric epoxidation, 6-(hydroxyphenyl)sulphonylbenzo[b]pyran, potassium channel opener, smooth muscle relaxant activity

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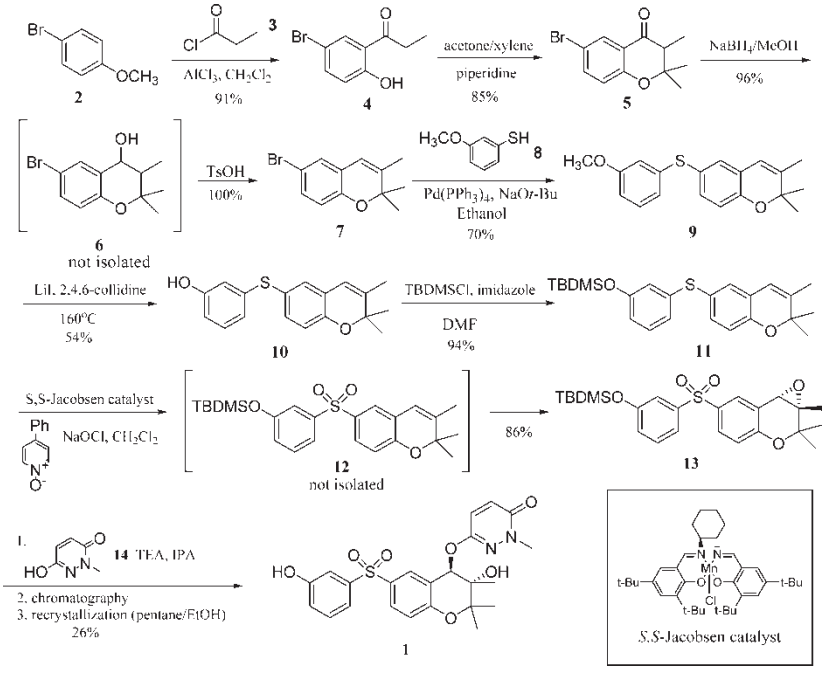
INTRODUCTION

6-(Hydroxyphenyl)sulphonylbenzo[b]pyran derivatives display smooth muscle relaxant activity by a mechanism that involves potassium channel opening.[1] They are therefore used in the treatment of conditions related to the altered tone and/or motility of smooth muscle, which can occur in the lung, bladder, gut, uterus, and cardiovascular system. Such conditions include chronic obstructive airways disease, asthma, urinary incontinence, irritable bowel syndrome, diverticular disease, oesophageal achalasia, and hypertension. Additionally, this family of compounds may be useful in the treatment of peripheral vascular disease, congestive heart failure, pulmonary hypertension, myocardial and cerebral ischaemia, angina, male pattern baldness, cardiac arrhythmia, skeletal muscle fatigue/paralysis (myotonic muscular dystrophy), glaucoma, epilepsy, tinnitus, vertigo, and dysmenorrhoea.

DISCUSSION

Compound **1** is a potent potassium channel opener that was developed in our laboratories and whose original synthesis is shown in Scheme 1. Friedel–Craft



Scheme 1. Original synthesis of compound **1**.

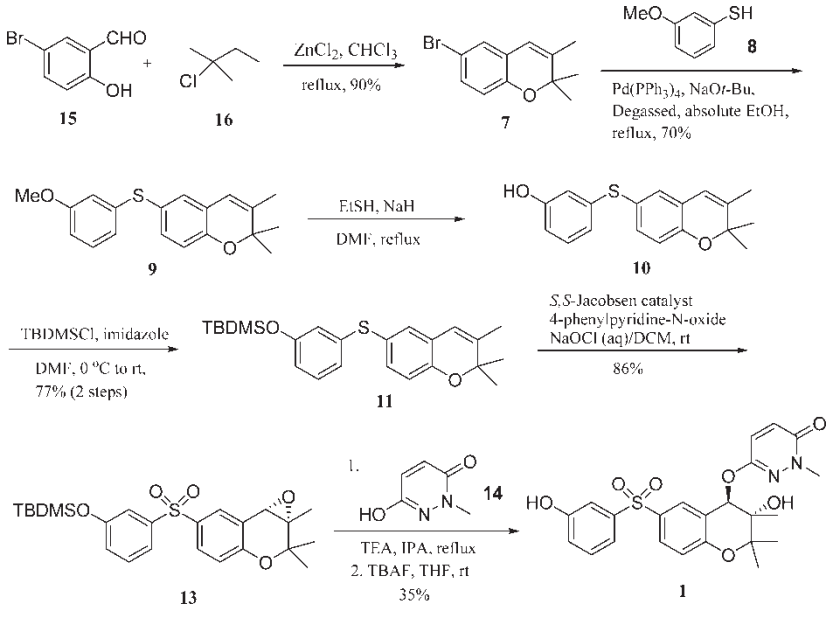
acylation of 4-bromoanisole (**2**) with propionyl chloride (**3**) in the presence of $AlCl_3$ in refluxing CH_2Cl_2 for 3 days afforded hydroxyketone **4,** which was converted to chromanone **5** in a mixture of acetone/xylenes with piperidine as base. This reaction was very sluggish and did not go to completion even after several days at reflux. Acetone/N,N-dimethylformamide (DMF)/piperidine at 80°C gave complete conversion after 2 days with yields around 90%. Chromanone **5** was then reduced with $NaBH_4$ in methanol and, after quenching with water and extracting the resulting alcohol **6** from the aqueous phase with toluene, it was treated with *p*-toluenesulfonic acid to give alkene **7** in quantitative yield. The coupling of **7** with 3-methoxythiophenol (**8**) in the presence of $Pd(Ph_3P)_4$ and NaO*t*-Bu in degassed ethanol at reflux provided methylether **9**.[2] Demethylation was effected with LiI in 2,4,6-collidine at 160°C to give phenol **10**.[3] Reprotection of the hydroxy group with *tert*-butyldimethylsilyl chloride (TBDMSCl) followed by asymmetric epoxidation using Jacobsen's catalyst (*S,S*)-(+)-*N,N′*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride and 4-methylpyridine-*N*-oxide in a biphasic mixture of aqueous NaClO and CH_2Cl_2 gave epoxisulfone **13**.[4] The reaction of **13** with 3 equivalents of 1-methyl-3,6-(1H,2H)-pyridazinedione (**14**) in refluxing isopropyl alcohol (IPA) for 48 h afforded crude **1**.[5] Purification by flash chromatography and recrystallization from pentane/ethanol gave compound **1** as a white solid.

The synthesis consisted of nine linear steps with a 16% overall yield. Significantly, there was no need for purification of the intermediates, which was a major advantage for any future scale-up work. On the other hand, the disadvantages of this route were that all the intermediates, except for **4** and **13,** were high-boiling oils, which made their purification by distillation difficult or impossible, and second, the last step required extensive purification.

An additional concern was methylether **9** deprotection, which, in some cases, gave incomplete conversion even after the addition of a very large excess of LiI.

A small-scale laboratory study of the chemistry revealed that a shorter or more convergent synthesis was necessary to viably scaleup the chemistry and that there was a need to simplify the purification process for the last step. To accomplish this, we first turned our attention to the synthesis of chromene **7**. A review of the literature revealed that chromenes such as **7** had either an ester or a keto group at the 3-position,[6] but the examples with alkyl groups were scarce, and their preparation required several steps.[7] However, one article was finally found where it was reported that the synthesis of 3-alkyl chromenes could be performed in one step starting from salicylaldehydes and chlorobutanes in the presence of $ZnCl_2$.[8]

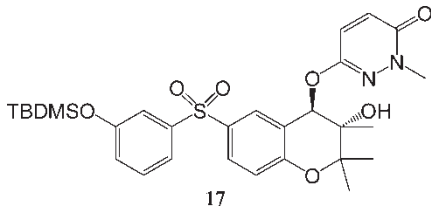
The new synthetic route (Scheme 2) started with the reaction between 5-bromosalicylaldehyde (**15**) and 2-chloro-2-methylbutane (**16**) in the presence of $ZnCl_2$ in refluxing $CHCl_3$ to give bromochromene **7** in 100% yield by mass and 90% purity by gas chromatography (GC) analysis. Attempts to distill this intermediate at high vacuum resulted in considerable



Scheme 2. Improved synthetic route for the preparation of **1**.

decomposition. Crude **7** was then treated as before with 3-methoxythiophenol (**8**) in the presence of $Pd(Ph_3P)_4$ and NaO*t*-Bu in refluxing ethanol. This gave rise to a crude methylether **9** that showed purity satisfactory for use without any further manipulations in the next step.

The harsh reaction conditions employed to demethylate **9** and the cost of LiI (up to 6 equivalents used) forced us to look for an alternative methodology. Attempts to accomplish this transformation through the use of $AlCl_3$/EtSH,[9] BBr_3,[10] or Cl_3MeSi/NaI[11] failed, giving either decomposition or incomplete reaction. However, it was discovered that a combination of either NaH or KO*t*-Bu and EtSH in refluxing *N,N*-dimethylformamide (DMF) for 1 h gave complete conversion to **10** in good yield and purity. Crude phenol **10** was reprotected with TBDMSCl/imidazole in DMF to give intermediate **11**, which was purified at this point by passing it through a short silica-gel pad to remove some highly polar impurities. Alkene **11** was then asymmetrically epoxidized, and the sulfide group oxidized to the sulfone following the previously tested method. The use of commercial bleach had no detrimental effect on the enantiomeric excess of the epoxidation and was considerably cheaper. Also, the use of 4-methylpyridine-*N*-oxide was crucial to obtain high enantioselectivity (>99% ee), because the enantiomeric excess when the far less expensive *N*-methylmorpholine-*N*-oxide was employed dropped to the upper 80s. When the reaction was run with the unprotected phenol or with the TMS-protected phenol, decomposition was observed.



17

Figure 1. Silyl protected impurity.

The last step required 36 h at reflux in IPA and 3 equivalents of 1-methyl-3,6-(1H,2H)-pyridazinedione (**14**) to consume the starting material. During previous runs, a less-polar impurity was detected by both thin-layer chromatography (TLC) and high performance liquid chromatography (HPLC) analysis (5–10%). This impurity was characterized as compound **17** (Fig. 1).

Because of the limited commercial availability of 1-methyl-3,6-(1H,2H)-pyridazinedione material and its high cost, we prepared it in our laboratories. A typical experimental procedure is as follows: to a solution of maleic anhydride (210 g, 2.14 mol) in glacial acetic acid (1 L) cooled in an ice-water bath (partial freezing may occur), methylhydrazine (114 mL, 2.14 mol) is added dropwise while the internal temperature is held below 20°C. After 15 min, the cooling bath is removed, and the mixture is allowed to warm to ambient temperature. After 1 h, the solvent is removed under vacuum to give a white solid, which is slurried in 500 mL of acetone for 1 h, filtered, washed with cold acetone (2 × 250 mL), and placed in a vacuum oven at 60°C for 2 days to give 233 g (86%) of 1-methyl-3,6-(1H,2H)-pyridazinedione as a white solid. Mp = 210–212°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.40 (s, 3H), 6.82 (d, $J = 9.7$ Hz, 1H), 6.99 (d, $J = 9.7$ Hz, 1H).

Other conditions that we tried for this last step (Cs_2CO_3/toluene/reflux, KO*t*-Bu/*t*-BuOH/reflux, K_2CO_3/DMF/100°C, NaOH/DMF/75°C) gave no reaction and/or partial decomposition.

We found that the addition of 1 equivalent of tetrabutylammonium fluoride as a 1 M solution in THF completed the deprotection. Crude **1** was subsequently purified by column chromatography and recrystallized from ethanol to give the desired product in 35% yield with chemical and optical purities (ee) better than 96% and 99% respectively. Attempts to purify **1** by alternative methods were unsuccessful because of the impurities produced during the last two steps of the synthesis.

CONCLUSION

In conclusion, a shorter synthetic route has been successfully developed for compound **1.** The scalability of this experimental protocol has been corroborated

by the preparation of multigram quantities of material through the implementation of numerous improvements with respect to the original synthesis.

EXPERIMENTAL

All reagents and solvents were used as received. 5-Bromosalicylaldehyde, ethanethiol, 4-phenylpyridine-*N*-oxide, Jacobsen's catalyst, and 1 M solution of tetrabutylammonium fluoride in THF were purchased from Aldrich Chemical Co. 2-Chloro-2-methylbutane was purchased from TCI America. Zinc chloride, sodium *tert*-butoxide, *tert*-butyldimethylsilyl chloride (TBDMSCl), and imidazole were purchased from Lancaster. Tetrakis(triphenylphosphine)palladium(0) was purchased from either Aldrich Chemical Co. or Strem. 3-Methoxybenzenethiol was purchased from Oakwood Products, Inc. Chloroform, *N,N*-dimethylformamide, dichloromethane, triethylamine, and isopropyl alcohol (IPA) were purchased from Mallinckrodt. Bleach was purchased from Chlorox Professional Products Company. Ethanol was purchased from Aaper. Silica gel was purchased from EM Science.

^{1}H NMR spectra were recorded on a Varian-Gemini-400 in either $CDCl_3$ or d_6-DMSO as both solvent and internal standard.

HPLC analyses to determine chemical purity were performed with a YMC Pack Pro C18 column with 60:40 20-mM ammonium formate (pH 5.0)–acetonitrile as mobile phase. Chiral HPLC analysis were performed with a Chiralpak AD column (250 × 4.6 mm, 10 μ) with 800:200:1:0.5 hexanes–IPA–TFA–diethylamine as mobile phase.

Positive and negative ion atmospheric pressure chemical ionization (APCI) mass spectra were obtained on a Micromass Platform LC mass spectrometer.

Melting points were determined with a Thomas Hoover melt-temp apparatus and are uncorrected.

Synthesis of Chromene 7

A mixture of $ZnCl_2$(141.2 g, 1.03 mol), 5-bromosalicylaldehyde (**15**) (208.6 g, 1.03 mol), and 2-chloro-2-methylbutane (**16**) (153 mL, 1.24 mol) in chloroform (1.5 L) was refluxed for 10 h under a nitrogen atmosphere. After cooling to 20°C, water (1 L) was added, and the two layers were separated. The aqueous layer was extracted with chloroform (2 × 200 mL), and the combined organic extracts were washed with brine (100 mL) and dried over $MgSO_4$. The solvent was removed to give 262.4 g (GC purity: 90% a/a) of chromene **7**as a very thick, dark purple oil, which was used in the next step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 6H), 1.83 (s, 3H), 6.01 (s, 1H), 7.01 (d, $J = 2.4$ Hz, 1H), 7.12 (dd, $J = 8.6$ Hz, $J = 2.4$ Hz, 1H). MS $m/z = 254$ $(M + H)^+$.

Synthesis of Methyl Ether 9

Chromene **7**(262.1 g, 1.03 mol), 3-methoxythiophenol (**8**) (174.0 g, 1.24 mol), and $Pd(Ph_3P)_4$(23.9 g, 20.7 mmol) were dissolved in degassed, absolute ethanol (2 L) under a nitrogen atmosphere. The mixture was cooled in an ice-water bath, and NaO*t*-Bu (332.0 g, 3.45 mol) was added in small portions over 30 min while the temperature inside of the flask was held below 25°C. The resulting mixture was refluxed for 18 h and then cooled to 20°C. Water (1 L) was added, and some of the solvent was removed under vacuum. The aqueous residue was extracted with hexanes (3 × 1 L), and the combined organic extracts were dried over $MgSO_4$. The solvent was removed under vacuum to give 215.4 g (HPLC purity: 82% a/a) of methyl ether **9**as a dark green oil, which was used in the next step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 6H), 1.83 (s, 3 H), 6.04 (s, 1H), 6.65–6.77 (m, 4H), 7.06–7.21 (m, 3H). MS $m/z = 313$ $(M + H)^+$.

Synthesis of Phenol 10

To a suspension of NaH (128.1 g, 3.19 mol) in dry DMF (1, 100 mL) under a nitrogen atmosphere, a solution of ethanethiol (220 ml, 2.97 mol) in dry DMF (620 mL) was added. The ice bath was removed, and after 10 m, a solution of methyl ether **9**(344.3 g, 1.10 mol) in dry DMF (400 mL) was added in one portion. The resulting mixture was refluxed for 1 h and then allowed to cool to 20°C. Water (2 L) was added, and the reaction was neutralized to pH 1 with 1 N HCl. The aqueous layer was extracted with *tert*-butyl methyl ether (3 × 1 L), and the combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was removed to give 132.7 g of phenol **10**as a brown oil (HPLC purity: 72% a/a). The crude was used without any further purification in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.43 (s, 3H), 1.83 (s, 3H), 6.03 (s, 1H), 6.57–6.60 (m, 3H), 7.05–7.20 (m, 3H). MS $m/z = 299$ $(M + H)^+$.

Synthesis of TBDMS-Protected Phenol 11

A solution of phenol **10** (278.1 g, 931 mmol) in dry DMF (830 mL) under a nitrogen atmosphere was cooled in an ice-water bath. Imidazole (146.0 g, 2.14 mol) was added, followed by TBDMSCl (147 g, 987 mmol) in small portions. The cooling bath was removed, and the mixture was stirred at room temperature for 72 h. Water (1 L) was added, and the aqueous layer was extracted with hexanes (3 × 1 L). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under vacuum to give a dark brown oil, which was chromatographed on silica gel (hexanes/

$CH_2Cl_2$2/1as mobile phase) to give 296.6 g (77% for two steps; HPLC purity: 92% a/a) of **11**as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.81 (s, 12H), 1.31 (s, 6H), 1.71 (s, 3H), 5.92 (s, 1H), 6.47–6.49 (m, 2H), 6.64–6.67 (m, 2H), 7.06-7.14 (m, 1H). MS $m/z = 413$ $(M + H)^+$.

Synthesis of Epoxide 13

Alkene **11**(225.0 g, 545 mmol), (*S*,*S*)-Jacobsen's catalyst [(*S*,*S*)-(+)-*N*, *N*′-bis(3, 5-di-*tert*-butylsalicylidene)-1, 2-cyclohexanediaminomanganese(III) chloride, 25.3 g, 40 mmol] and 4-methylmorpholine-*N*-oxide (24.3 g, 142 mmol) were dissolved in CH_2Cl_2 (1.3 L), and the flask was cooled in an ice-water bath. Commercial bleach (NaClO content: 6.15%; 7.75 L) was added over 1.5 h while the internal temperature was held below 20°C. The cooling bath was removed, and the dark brown mixture was allowed to reach ambient temperature and vigorously stirred at this temperature for 18 h. The resulting thick emulsion was filtered through-celite®, and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 1 L), and the combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was removed to give 215.9 g of epoxide **13** as a brown solid (HPLC purity: 89% a/a) that was used in the next step without any further purification. ^{1}H NMR (400 MHz, CDCl3) δ 0.00 (s, 6H), 0.77 (s, 12H), 1.07 (s, 3H), 1.31 (s, 3H), 1.35 (s, 3H), 3.51 (s, 1H), 6.67 (d, $J = 8.6$ Hz, 1H), 6.77–6.81 (m, 1H), 7.12–7.17 (m, 2H), 7.26–7.29 (m, 1H), 7.57 (dd, $J = 2.4$ Hz, $J = 8.5$ Hz, 1H), 7.69 (d, $J = 2.4$ Hz, 1H). MS $m/z = 461$ $(M + H)^+$.

Synthesis of 1

Epoxide **13** (92.9 g, 202 mmol), 1-methyl-3,6-(1H,2H)-pyridazinedione (**14**) (76.4 g, 605 mmol), and triethylamine (85 ml, 605 mmol) were dissolved in isopropyl alcohol (550 mL), and the mixture was refluxed for 28 h and then cooled to 20°C. Thin-layer chromatographic (TLC) analysis (ethyl acetate/methanol 95/5) showed complete consumption of the starting material and a spot corresponding to the *tert*-butyldimethylsilyl-protected intermediate **17**. Tetrabutylammonium fluoride solution (1 M) in THF (200 mL) was added, and the mixture was stirred at room temperature for 30 min to complete the removal of the TBDMS protecting group. The solvent was removed under vacuum to give a dark brown oil which was dissolved in ethyl acetate (2 L), washed with water (1 × 1.5 L, 3 × 500 mL), and brine, and dried over $MgSO_4$. The solvent was removed to give a dark brown solid, which was purified by chromatography on silica gel (acetonitrile/methanol, gradient elution) to give 57.6 g of a beige solid. This solid was dissolved in ethanol (500 mL), filtered to remove some insoluble material,

and concentrated to a final volume of about 200 mL. The solution was placed in a freezer at -5°C for 20 h and the solid thus obtained was filtered, washed with cold ethanol (2×20 mL), and dried under vacuum at 20°C and 17 torr to give 33.5 g (35% yield) of **1** as an off-white solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.99 (t, $J = 7.1$ Hz, 3H), 1.15 (s, 3H), 1.28 (s, 3H), 1.34 (s, 3H), 3.35–3.40 (m, 2H), 3.54 (s, 3H), 4.31 (t, $J = 5.1$ Hz, 1H), 5.35 (s, 1H), 5.74 (s, 1H), 6.92–7.00 (m, 3H), 7.12-7.13 (m, 1H), 7.19–7.34 (m, 3H), 7.68 (dd, $J = 2.5$ Hz, $J = 8.8$ Hz, 1H), 7.76 (d, $J = 2.2$ Hz, 1H), 10.19 (s, 1H). MS $m/z = 473$ $(M + H)^+$. Anal. calcd. for $C_{23}H_{24}N_2O_7S$: C, 58.46; H, 5.12; N, 5.93; S, 6.79. Found: C, 58.09; H, 5.10; N, 5.93; S, 6.86. Mp: 138–165°C. HPLC chemical purity: 97.9%; HPLC optical purity: >99.5% (ee).

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