An efficient synthesis of *endo*-bicyclo[3.2.0]hept-6-en-3-yl benzoates

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Abstract

An efficient method for the synthesis of difficultly available *endo*-bicyclo[3.2.0]hept-6-en-3-yl benzoates was successfully developed via esterification of benzoyl chloride with bicyclo[3.2.0]hept-6-en-3-ol, which can be obtained almost exclusively with *endo* configuration by selective reduction of bicyclo[3.2.0]hept-6-en-3-one with lithium aluminum hydride or L-Selectride.

Keywords: Photochemical cyclization, bicyclo[3.2.0]hept-6-en-3-yl benzoate, lithium aluminum hydride, esterification

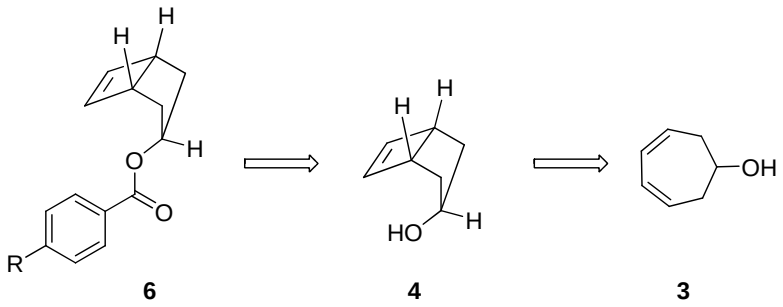
Introduction

Bicyclo[3.2.0]heptene derivatives have been widely used in organic synthesis and in polymer chemistry, especially for ring-opening metathesis polymerization (ROMP), because these strategies can provide very powerful and broadly applicable methods for the synthesis of a large variety of polymers and macromolecular materials.[1, 2] The cyclobutene skeleton in these structures can be constructed by intramolecular photochemical [2+2] cycloaddition in a corresponding diene. But this reaction often affords the product as a mixture consisting of *endo*- and *exo*- diastereomers, recalling that the *endo* product is the one in which the substituent points toward the double bond and the *exo* product is the one in which the substituent points away from the double bond.[3] In many cases, applications involving these compounds request them to be diastereomerically pure, especially when studying the tacticity of polymers resulting from ROMP of these bicyclic alkene derivatives.[4-7] However, most of the present methods for the synthesis of bicyclo[3.2.0]heptene derivatives suffer from low selectivity, harsh reaction condition, use of rare and expensive catalysts, tedious work-up, etc. Therefore, development of a

mild, more selective and practical method for this transformation is still in demand. Herein we wish to present an efficient synthesis of diastereomerically pure *endo*-bicyclo[3.2.0] hept-6-en-3-yl benzoates with full characterization, which have not been reported to the best of our knowledge.

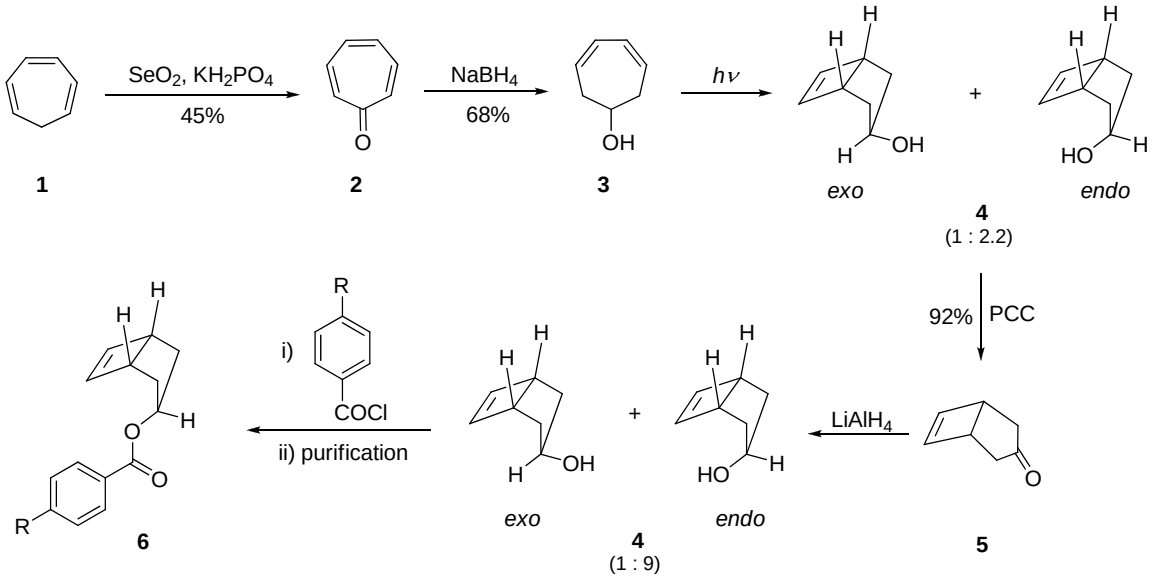
Results and Discussion

In order to obtain diastereomerically pure *endo*-bicyclo[3.2.0]hept-6-en-3-yl benzoates **6**, it is necessary to make the corresponding *endo*-bicyclo[3.2.0]hept-6-en-3-ol, **4**, available, in which the bicycloheptene skeleton can be constructed by intramolecular photochemical cyclization from 3,5-cycloheptadienol, **3** (Scheme 1).



6 **4** **3**

Scheme 1



Scheme 2

As shown in Scheme 2, oxidation of cycloheptatriene with SeO_2 in the presence of KH_2PO_4 afforded tropone **2** in 45% yield.[8] Reduction of **2** with $NaBH_4$ gave 3, 5-cycloheptadienol, **3**, in 68% yield. Intramolecular photochemical cyclization of **3** gave a mixture consisting of *endo* and *exo* diastereomers in a ratio of 2.2:1 (based on ^{1}H NMR analysis on the characteristic olefinic or bridgehead proton.[9] It is rather difficult to separate these two epimers by common purification techniques such as fractional distillation and column chromatography. To circumvent this problem, we transformed this mixture into ketone **5** in 92% yield by oxidation with pyridinium chlorochromate (PCC). Reduction of **5** with lithium aluminum hydride (LAH) significantly increased the ratio (*endo*:*exo*) up to 9:1 (Figure 1).

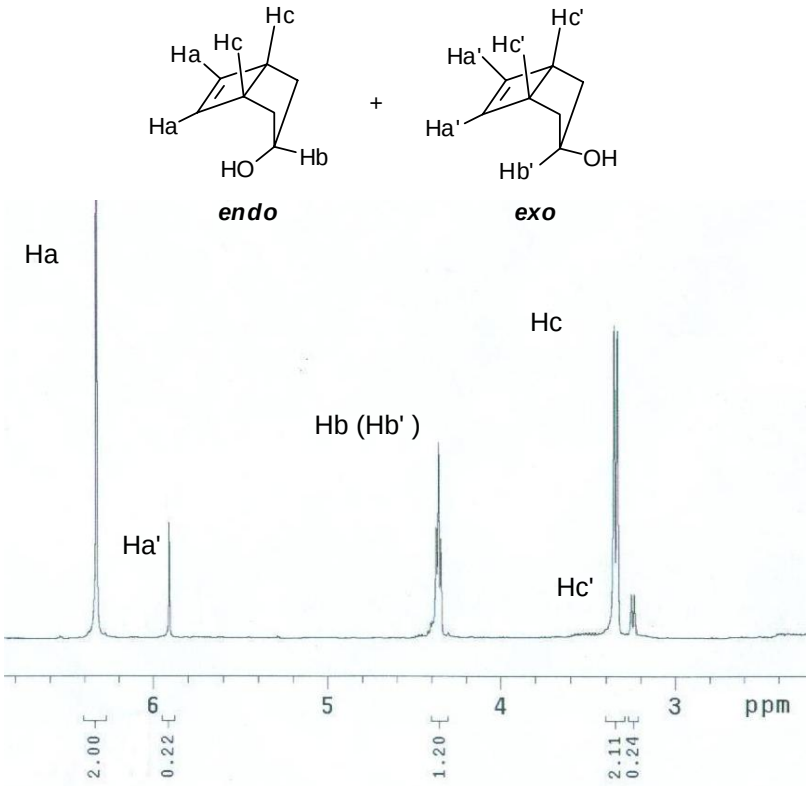
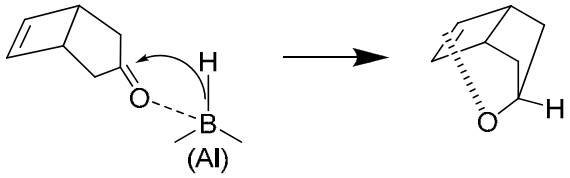


Figure 1. Partial ^{1}H NMR of the mixture (*endo*:*exo,* 9:1) resulted from reduction with $LiAlH_4$.

When L-Selectride ($LiBH(s\text{-}Bu)_3$) was employed, this reaction almost exclusively afforded the *endo* epimer. This result may be ascribed to the fact that the more bulky hydride would attack the carbonyl more predominantly from the least hindered side of the bicyclic skeleton, thus the *endo* is more favored. ^{1}H NMR analysis shows that the olefinic protons of the *endo* appear at lower field (6.33 ppm), comparing with those of the *exo* at 5.91 ppm (Figure 1). This is consistent with an interaction between the cyclobutene double bond and the hydroxyl group in the *endo*-configuration, which effectively removes electrons from the double bond (Scheme 3).[10]



Scheme 3

Although L-Selectride can give higher selectivity, we still chose $LiAlH_4$ as the reductant, considering that L-Selectride is very expensive and that $LiAlH_4$ can also give a practical selectivity (90%) for the following synthesis. Thus the mixture resulting from $LiAlH_4$ (*endo*: *exo* 9:1) was directly employed for esterification with various benzoyl chlorides. The diastereomerically pure *endo*-bicyclo[3.2.0]hept-6-en-3-yl benzoates **6** can be isolated in moderate to good yields (65–85%) by crystallization in most cases. The results are summarized in Table 1.

Table 1. Synthesis of *endo*-bicyclo[3.2.0]hept-6-en-3-yl benzoates **6** via esterification of benzoyl chloride with bicyclo[3.2.0]hept-6-en-3-ol

Product **6**	R	Reaction time [h][a]	Yield [%][b]	m. p. [°C]
6a	NO_2	1.5	85	115-116
6b	Br	2.0	83	104-105
6c	H	3.0	65[c]	oil
6d	Me	3.0	74	55-57
6e	OMe	4.0	72	59-61

[a] Monitoring time by TLC analysis. [b] Isolated yield by crystallization of the crude product from petroleum /ethyl acetate (v/v = 15:1) at –20 ºC. [c] Isolated by preparative TLC.

To further confirm the *endo*-configuration, we performed an X-ray single crystal analysis using **6b** as an example, in which the benzoate moiety obviously points toward the carbon-carbon double bond (Figure 2).

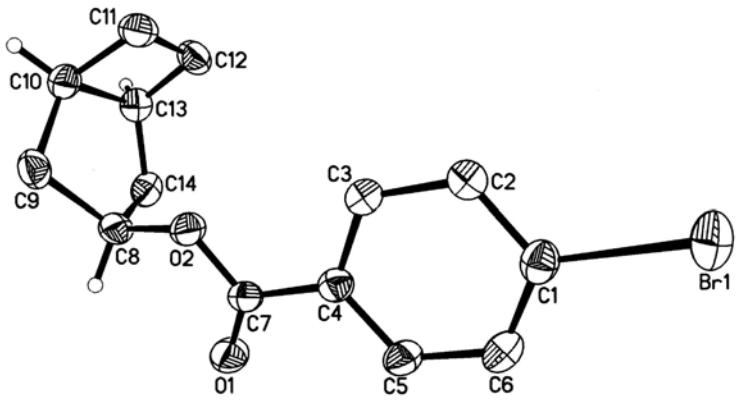


Figure 2. ORTEP view of **6b** showing the atom labeling (CCDC 714709). Selected crystal data: Triclinic, space group P-1; unit cell dimensions (a = 6.6718(2) Å, α = 74.3740 (10) °; b = 8.2358 (2) Å, β = 88.067 (2) °; c = 11.6390 (3) Å, γ = 83.0370 (10) °); Volume 611.36(3) Å^3, Z = 2; density (calculated) 1.593 Mg/m^3. Selected interatomic distances (Å): C11–C12 1.310 (4), C10–C13 1.563 (3), C10–C11 1.512 (3), C9–C10 1.520 (3), C8–C9 1.523 (4), O2–C8 1.458 (3); selected interatomic angles: C7–O2–C8 117.33 (17), O2–C8–C9 107.9 (2), C9–C10–C11 116.5 (2).

Conclusions

In summary, we have developed an efficient synthesis of difficultly available diastereomerically pure *endo*-bicyclo[3.2.0]hept-6-en-3-yl benzoates, in which the precursor *endo*-bicyclo[3.2.0]hept-6-en-3-ol was prepared by selective reduction of bicyclo[3.2.0]hept-6-en-3-one with lithium aluminum hydride. This synthetic strategy is cost-beneficial with easy work up. Furthermore, all the products were well characterized by IR, NMR and HR-MS, and the *endo*-configuration was further confirmed by X-ray diffraction.

Experimental Section

General Procedures. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Varian 400 spectrometers in $CDCl_3$ solutions. Chemical shifts (δ) are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (7.26 ppm for ^{1}H and 77.00 ppm for ^{13}C). IR spectra were recorded on a Thermo Nicolet Avatar 360 E. S. P. FT-IR spectrometer in KBr film. All melting points were determined on a Fargo MP-1D apparatus without correction. High-resolution mass spectra (HRMS) were recorded on a Jeol SX-102A spectrometer with EI, ESI or API mode.

X-ray crystallographic structure of 6b. Diffraction measurements were made on a Nonius

Kappa CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å), operating at 295 K, over the θ range 3.54–27.46°. No significant decay of the crystal was observed during the data collection. Data were processed on a PC using the SHELXTL software package. The structure of **6b** was solved using direct methods and refined by full-matrix least squares on the F^2 value. All non-hydrogen atoms were refined anisotropically. The positions of hydrogen atoms were identified by calculation, and their contributions to structure factors were included. The final indices were R_1= 0.0344, wR_2 = 0.0876 with goodness-of-fit on F^2 = 1.020. Supplementary crystallographic data (CIF) have been deposited with the Cambridge Structural Database as CCDC-714709. Copies can be obtained free of charge on application to the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax: (internat.) +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

Tropone (**2**)**.** A solution containing cycloheptatriene, **1** (51.6 g, 0.56 mol), SeO_2 (63.6 g, 0.574 mol), KH_2PO_4 (16.2 g, 0.118 mol), H_2O (200 mL) and 1, 4-dioxane (400 mL) is kept refluxing under nitrogen atmosphere for 20 h. After the black suspension is cooled to room temperature, 200 mL of water is added and the mixture is filtered through Celite. The filtrate is extracted with CH_2Cl_2 (2 × 300 mL), washed with saturated $NaHCO_3$ (150 mL) and dried (Na_2SO_4). The solvent is removed under reduced pressure and the resulting black liquid is fractionally distilled (90–92 °C at 4.0 mm; lit.[8] 62–65°C at 0.25 mm) to give the product as a pale yellow oil (26.4 g, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84–6.89 (m, 4 H), 6.97–7.02 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 135.6, 141.2, 187.1; IR (KBr) 3004, 1635, 1582, 1518, 1473, 1213 cm^{-1}.

3,5-Cycloheptadienol (**3**)**.** To a solution containing tropone **2** (3 g, 0.028 mol), MeOH (65 mL) and distilled water (10 mL) at 0 °C is slowly added $NaBH_4$ (2.0 g, 0.053 mol) with vigorous stirring. After addition, the mixture is stirred vigorously for 2 h. The remaining hydride was then decomposed by the dropwise addition of glacial acetic acid (10 mL). After neutralization with $NaHCO_3$, the mixture was extracted with ether, dried (Na_2SO_4) and concentrated to distill (52–55 °C at 4 mm; lit.[9] 73 °C at 25 mm), affording the product as a colorless liquid (1.9 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85–1.88 (m, 1 H), 2.55–2.58 (m, 4 H), 4.22 (m, 1 H), 5.64–5.70 (m, 2 H), 5.88–5.91 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.4, 68.3, 126.1, 127.9; IR (KBr) ν 3360, 2868, 1160, 1063, 722 cm^{-1}.

Bicyclo[3.2.0]hept-6-en-3-ol (**4**)**.** A solution of 3,5-cycloheptadienol 3 (2.2 g, 20.0 mmol) in anhydrous ether (800 mL) was bubbled with nitrogen for 30 min and then irradiated for 4 h with a quartz jacketed Hanovia immersion lamp. Removal of the ether afforded the crude photoproduct bicyclo[3.2.0]hept-6-en-3-ol consisting of the *endo*/*exo* epimers with a ratio of 2.2:1 (based on ^{1}H NMR analysis), which was used in the next oxidation step without purification.

Bicyclo[3.2.0]hept-6-en-3-one (5). To a suspension of pyridinium chlorochromate (4.75 g, 22.0 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added a solution of the above bicyclo[3.2.0]hept-6-en-3-ol (**4**) dissolved in CH_2Cl_2 (15 mL). After 2 h at RT, the supernatant liquid was poured into ether (100 mL), the residual was extracted with ether (2 × 50 mL), and the combined ethereal phases were filtered over silica gel and eluted with ether. Removal of the collected solvents gave the

crude product as colorless liquid, which was used in the next reduction step without purification. It can be further purified by fraction distillation (72–74 ^{o}C at 10 mmHg). Yield 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15–2.23 (m, 2 H), 2.35–2.41 (m, 2 H), 3.47 (d, J = 7.6 Hz, 2 H), 6.10 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.1, 42.6, 140.2, 217.3; IR (KBr) ν 2933, 2864, 1738, 1408, 1153, 969 cm^{-1}; HR-MS (EI) Calcd for C_7H_8O (M^+): 108.0575, Found: 108.0573.

General procedure for the synthesis of *endo*-bicyclo[3.2.0]hept-6-en-3-yl benzoate (6)

To a stirring solution containing bicyclo[3.2.0] hept-6-en-3-ol (1.10g, 10 mmol), DMAP (trace) and pyridine (15 mL) at 0 ^{o}C was added slowly with a solution containing benzoyl chloride **5** (12 mmol) in dry CH_2Cl_2. After addition, the reaction was kept stirring at RT overnight. The reaction mixture was washed with diluted HCl, saturated $NaHCO_3$ and water, dried and concentrated to afford the crude product, which was further purified by crystallization from petroleum /ethyl acetate (v/v = 15:1) at –20 ºC. Compound **6c** was isolated by preparative TLC on silica gel using petroleum /ethyl acetate (5:1) as an eluent.

***endo*-Bicyclo[3.2.0]hept-6-en-3-yl 4-nitrobenzoate (6a).** Yield 85%; mp 114–116 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84–1.91 (m, 2 H), 2.03 (d, J = 15.2 Hz, 2 H), 3.38 (d, J = 6.8 Hz, 2 H), 5.61 (m, 1 H), 6.16 (s, 2 H), 8.16 (d, J = 8.0 Hz, 2 H), 8.27 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.9, 48.1, 81.0, 127.5, 129.8, 130.9, 131.4, 140.6, 164.9; IR (KBr) ν 2964, 2932, 1708, 1601, 1525, 1343, 1270, 1120, 1012, 871, 841, 718 cm^{-1}; HR-MS (FAB) Calcd for $C_{14}H_{14}NO_4$ (M+1): 260.0923, Found: 260.0922.

***endo*-Bicyclo[3.2.0]hept-6-en-3-yl 4-bromobenzoate (6b).** Yield 83%; mp 103–105 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89–1.94 (m, 2 H), 2.07 (d, J = 15.2 Hz, 2 H), 3.42 (d, J = 6.8 Hz, 2 H), 5.66 (brs, 1 H), 6.19 (s, 2 H), 7.56 (d, J = 6.8 Hz, 2 H), 7.85 (d, J = 6.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.9, 48.0, 81.8, 123.3, 130.5, 136.2, 140.6, 150.2, 163.8; IR (KBr) ν 2933, 2910, 1708, 1588, 1218, 1103, 1009, 845, 756 cm^{-1}; HR-MS (API) Calcd for $C_{14}H_{14}O_2{}^{79}Br$ (M+1): 293.0177, Found: 293.0176.

***endo*-Bicyclo[3.2.0]hept-6-en-3-yl benzoate (6c).** Yield 65%; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84–1.91 (m, 2 H), 2.04 (d, J = 14.8 Hz, 2 H), 3.39 (d, J = 7.2 Hz, 2 H), 5.63 (m, 1 H), 6.19 (m, 2 H), 7.40–7.44 (m, 2 H), 7.52–7.56 (m, 1 H), 8.00–8.02 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.9, 48.1, 80.7, 128.1, 129.4, 130.9, 132.5, 140.6, 165.7; IR (KBr) ν 2961, 2930, 1709, 1603, 1448, 1315, 1273, 1110, 1025, 854, 718 cm^{-1}; HR-MS (API) Calcd for $C_{14}H_{15}O_2$ (M+1): 215.1072, Found: 215.1066.

***endo*-Bicyclo[3.2.0]hept-6-en-3-yl 4-methylbenzoate (6d).** Yield 74%; mp 55–56 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83–1.90 (m, 2 H), 2.03 (d, J = 15.2 Hz, 2 H), 2.40 (s, 3 H), 3.38 (d, J = 7.2 Hz, 2 H), 5.61 (m, 1 H), 6.18 (m, 2 H), 7.21 (d, J = 8.0 Hz, 2 H), 7.89 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 34.9, 48.2, 80.4, 128.1, 128.8, 129.4, 140.6, 143.0, 165.8; IR (KBr) ν 2960, 2928, 1710, 1600, 1310, 1270, 1110, 858, 723 cm^{-1}; HR-MS (API) Calcd for $C_{15}H_{17}O_2$ (M+1): 229.1229, Found: 229.1233.

***endo*-Bicyclo[3.2.0]hept-6-en-3-yl 4-methoxybenzoate (6e).** Yield 72%; mp 59–60 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85–1.90 (m, 2 H), 2.03 (d, J = 15.2 Hz, 2 H), 3.38 (d, J = 7.2 Hz, 2

H), 3.86 (s, 3 H), 5.61 (t, *J* = 5.6 Hz, 1 H), 6.18 (s, 2 H), 6.91 (dd, *J* = 6.6, 2.2 Hz, 2 H), 7.96 (dd, *J* = 6.6, 2.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 162.7, 140.5, 131.4, 123.4, 113.4, 80.3, 55.4, 48.2, 34.9; IR (KBr) ν 2963, 2930, 1710, 1605, 1510, 1253, 1164, 1100, 1028, 848, 772 cm^{-1}; HR-MS (API) Calcd for $C_{15}H_{17}O_3$ (M+1): 245.1178, Found: 245.1178.

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