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Studies directed toward the total synthesis of azaspiracid. Construction of the C_1–C_{19} carbon backbone and synthesis of the C_{10}, C_{13} nonnatural transoidal bisspirocyclic ring system†

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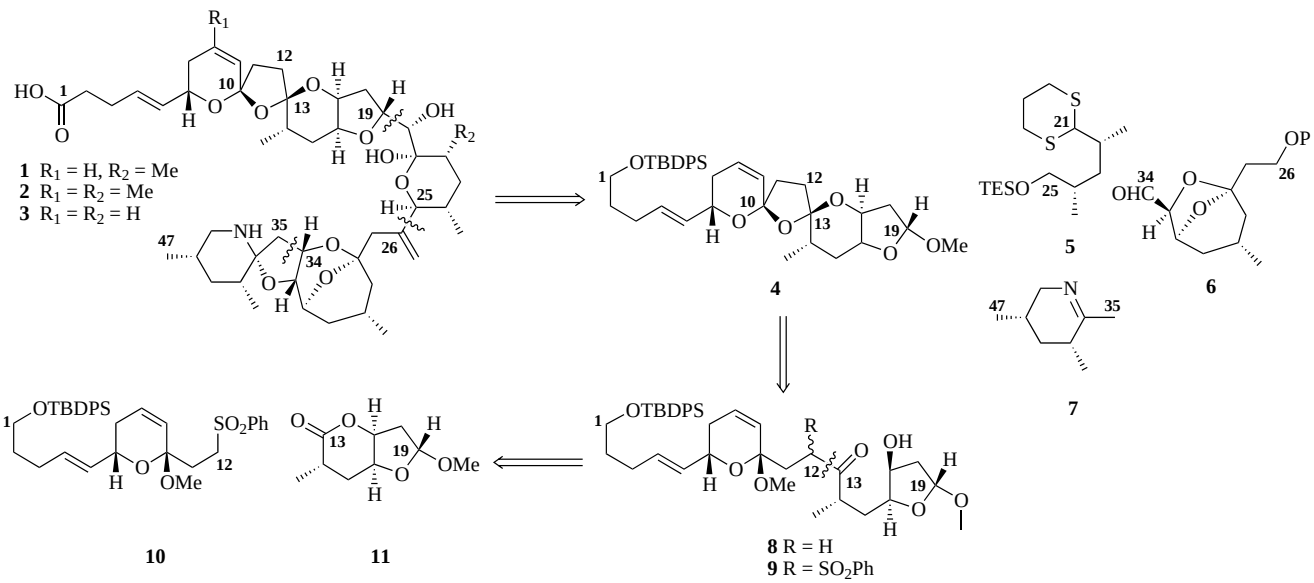
Abstract—The efficient entry to the C_1–C_{19} carbon backbone of azaspiracid is outlined utilizing a key Julia coupling strategy. Spirocyclization of a C_{12} sulfone substrate induced formation of the unprecedented, nonnatural transoidal bisspiroketal. Construction of the bisspirocyclic array at C_{10} and C_{13}, in the absence of the C_{12} sulfone, led to formation of the cisoidal orientation of the bisspirocycle, with the nonnatural stereochemistry at C_{13}. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Azaspiracid (**1**) and its related structures, azaspiracid-2 (**2**) and azaspiracid-3 (**3**), have begun to garner significant synthetic attention[1,2] due to their challenging spirocyclic structures as well as their considerable toxicity in mice.[3,4] Our laboratory has recently disclosed the construction of the C_1–C_{12}, C_{13}–C_{19} and C_{21}–C_{25} portions of azaspiracid.[1a] In this communication, we report the synthesis of the C_1–C_{19} carbon framework of azaspiracid (**1**) using a sulfone coupling strategy (Scheme 1). In addition, the powerful controlling influence of the C_{12} sulfone functionality in the bisspirocyclization is investigated for the construction of the transoidal[5] orientation of the bisspiroketal. Previous work in this area[1b,2b,2c] has only disclosed the formation of the



Scheme 1.

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† Dedicated to Professor Alex T. Rowland on the occasion of his retirement.

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cisoidal[5] (10*R*,13*S*) stereochemistry in the bisspirocyclization.

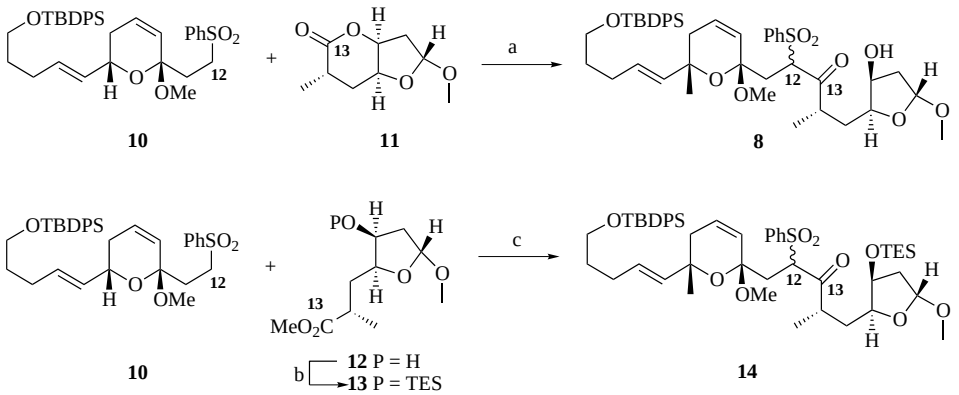
2. Construction of $C_{12,13}$ linkage

Our initial strategy[1a] for the construction of the key $C_{12,13}$ sigma bond involved an anionic coupling of sulfone **10** with lactone **11** to yield the keto sulfone **8** directly. Although this strategy did prove modestly successful, we were discouraged by the disappointing yields (15–20%) in this transformation (Scheme 2). A considerable amount of decomposition of the lactone **11** was observed under all reaction conditions. One potential alternative to **11** was the previously described[1a] ester **13**. While the ester **13** did provide an improvement in the production of the required keto sulfone **14**, the yields (up to 40%) continued to fall short of desirable levels.

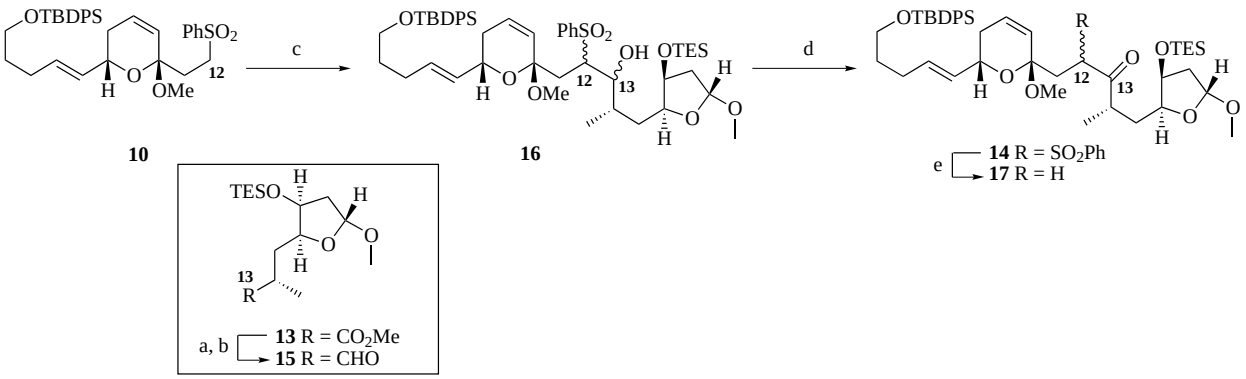
A Julia coupling[6] strategy with aldehyde **15** might prove to be a more reliable approach for the formation of the $C_{12,13}$ linkage (Scheme 3). The straightforward conversion of the ester **13** to the aldehyde **15** was accomplished in 93% overall yield. Subsequent Julia coupling of aldehyde **15** with sulfone **10** did provide the desired $C_{12,13}$ linkage in a gratifying 99% yield, as a mixture of three of the four possible diastereomers. Conversion of the Julia adduct **16** to the desired keto sulfone **14** is worthy of further comment. Attempted oxidation of **16** using Swern conditions[7] or Dess–Martin's periodinane[8] led to a complex mixture of products. Fortunately, TPAP[9] oxidation proved a feasible method for the synthesis of ketone **14**. It should also be noted that epimerization at C_{12} of the keto sulfone **14** occurred under the slightly basic media of the TPAP oxidation to provide an inseparable 1:1 mixture of sulfone epimers. Subsequent Na/Hg reduction[10] of the keto sulfone **14** yielded the desired ketone **17**.

3. Bisspirocyclization

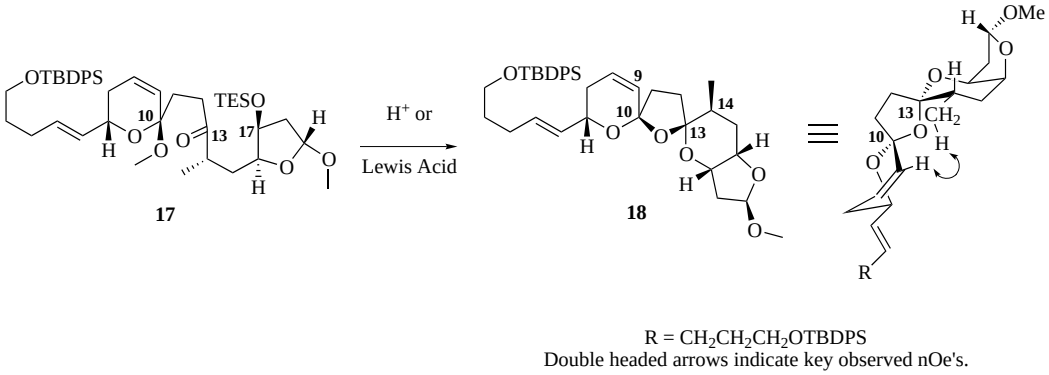
Our approach for the construction of the crucial C_{10} and C_{13} spirocyclic linkages invoked a preorganization strategy by establishing the surrounding ring systems prior to spirocyclization. It was hoped that these neighboring structural buttresses should provide a favorable environment for spirocyclization to the desired stereochemical relationships. Treatment of ketone **17** under a variety of mildly acidic conditions or Lewis acid conditions (e.g. PPTS, PTSA, $BF_3{\cdot}Et_2O$) did induce desilylation at C_{17} with in situ cyclization to form the bisspiroketal **18** as the only isolable spirocycle (Scheme 4).



Scheme 2. *Reagents and conditions*: (a) LDA, THF, −78°C, then **11**, 20%; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, −78°C, 93%; (c) LDA, THF, −78°C, then **13**, −78 to −10°C, 40%.



Scheme 3. *Reagents and conditions*: (a) DIBAL-H, CH_2Cl_2, −78°C, 99%; (b) TPAP, NMO, CH_2Cl_2, mol. sieves, 93%; (c) LDA (1.15 equiv.), THF; **15** (1.2 equiv.), −78°C, 99%; (d) TPAP, NMO, CH_2Cl_2, mol. sieves, 81%; e) 5% Na/Hg, THF, MeOH, −10°C, 88%.

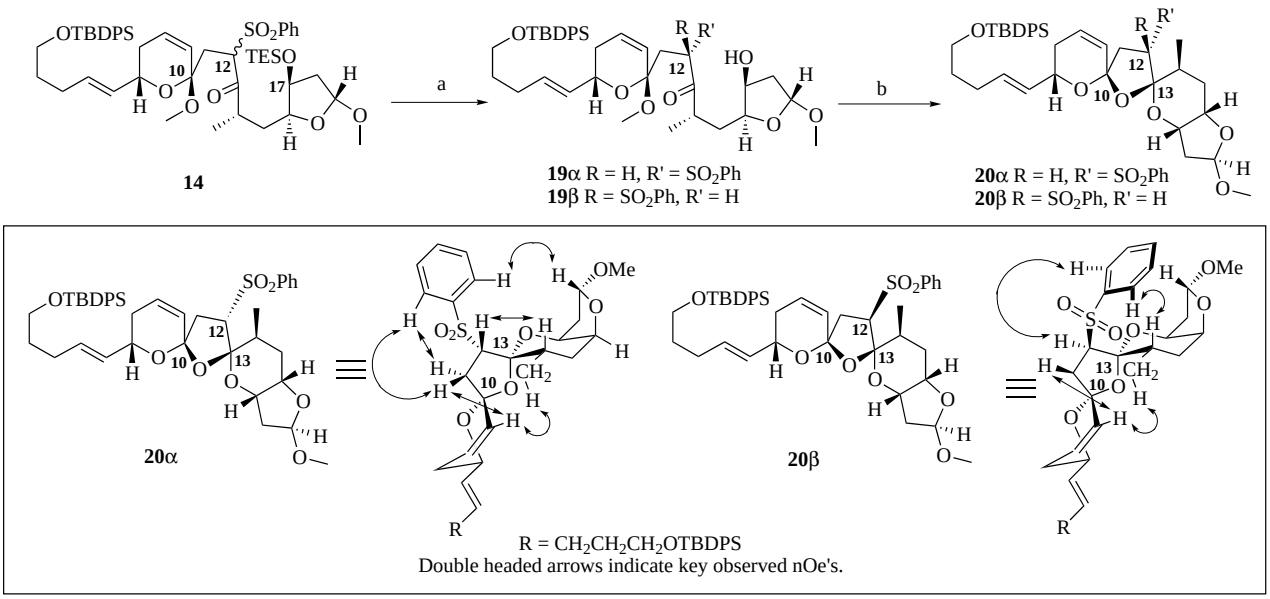


Scheme 4.

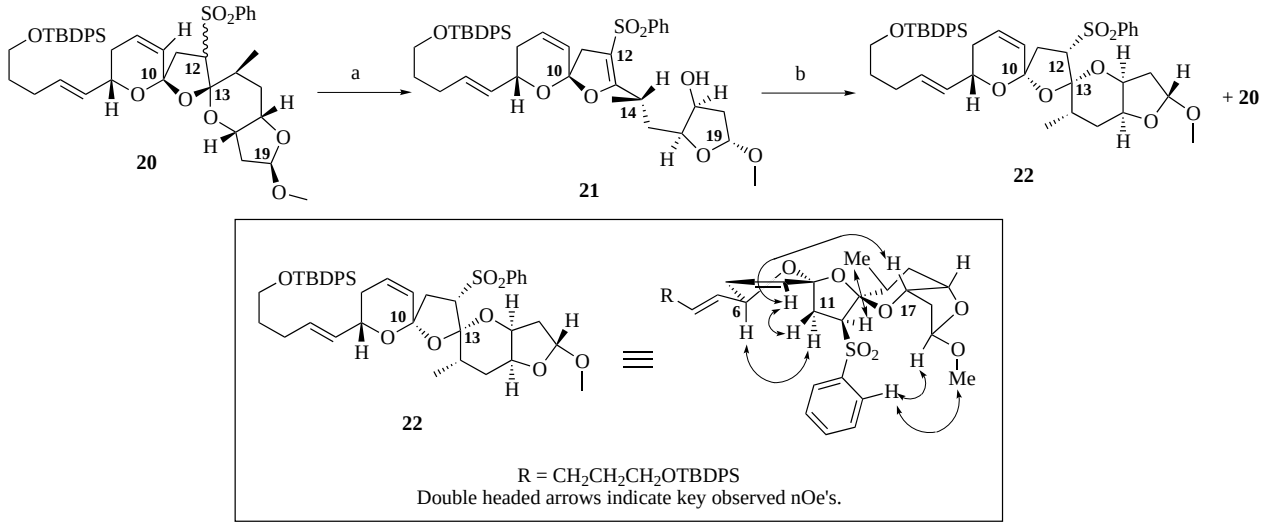
The stereochemistry of **18** was established by NOESY and COSY correlations as the undesired 10*R*,13*S* or cisoidal[5] stereochemistry. These results[1b] are in good agreement with Dounay and Forsyth[2b,2c] who independently observed a similar preference for the 10*R*,13*S* stereoisomer. In addition, our own high level ab initio calculations [HF/6-31G(d) and B3LYP/6-31G(d)||HF/6-31G(d)] show that the cisoidal isomer **18** is up to 7 kcal/mol more stable. Based on the experimental and theoretical data, an alternate strategy for the construction of the transoidal bisspirocycle was required.

One potential option lies in the immediate precursor to the ketone **17**: keto sulfone **14**. The steric bulk imparted by the C_{12} sulfone moiety should have a dramatic impact on the reactivity of any oxonium ion derived from **14**.[11] As stated previously, the keto sulfone **14** exists as a 1:1 inseparable mixture at C_{12}. Fortunately, removal of the C_{17} TES protecting group under buffered TBAF conditions[12] did provide a separable 1:1 ratio of the *R* and *S* stereoisomers at C_{12} (Scheme 5). Treatment of the separated compounds **19**α and **19**β under acidic conditions (CSA, MeCN) produced the cisoidal (10*R*,13*R*)[13] bisspirocycle **20**α and **20**β, respectively, as single epimers. These structures were once again assigned via NOESY and COSY 2D NMR experiments. In order to correlate the bisspirocycle **20** to the previously described cisoidal (10*R*,13*S*) bisspirocycle **18**, the C_{12} sulfone function was removed under Na/Hg conditions to provide **18** in an unoptimized 60% yield. It should also be noted that submission of keto sulfone **14**, as the 1:1 mixture at C_{12}, to the identical acidic conditions (CSA, MeCN) resulted in the formation of the cisoidal bisspirocycle **20** as a 1:1 mixture at C_{12} (72% yield).

As considerable solvent effects have been observed in bisspirocyclizations,[14] it was hoped that treatment of keto sulfone **14** or **19** under alternate acidic conditions (e.g. PPTS, $BF_3{\cdot}Et_2O$, CSA) in a variety of solvents (e.g. *t*-BuOH, CH_2Cl_2, PhH) would provide access to the transoidal orientation of the bisspiroketal. Only camphorsulfonic acid (CSA) in benzene led to the formation of a new bisspirocycle as a minor product (≈5–10%), which was identified as the nonnatural



Scheme 5. *Reagents and conditions*: (a) TBAF, HOAc, THF, 75%; (b) CSA, MeCN, 82% for **20**α, 60% for **20**β.



Scheme 6. *Reagents and conditions*: (a) *n*-BuLi, THF, −78°C, 83%; (b) CSA, PhMe 43% of **22**, 49% of **20**.

transoidal[5] (10*S*,13*R*) bisspirocycle **22**. All other attempted conditions continued, however, to provide the cisoidal (10*R*,13*R*) spirocycle as the predominate product. In order to access an alternate bisspirocyclization precursor, the sulfone **20** was treated with *n*-BuLi at −78°C, which coaxed β-elimination to yield the elaborate enol ether **21** (Scheme 6). It was imperative that this reaction be quenched at −78°C. If the reaction was allowed to warm to −10°C, the alkoxide readded to the C_{13} alkene to provide the sulfone **20**. Next, spirocyclization of the alcohol **21** under acidic conditions in toluene induced formation of the nonnatural transoidal spirocycle **22**, with the 10*S*,12*R*,13*R* stereochemistry, along with nearly equal amounts (4:5) of the cisoidal (10*R*,13*R*) spiroketal **20** in an overall 92% yield.[15] While the spirocycle **22** was isolated as a single isomer at C_{12}, the epimeric ratio at C_{12} in the previously observed spiroketal **20** was approximately 3:1 favoring the 12*R* or α sulfone. The stereochemistry of **22** was established via COSY and ROESY correlations, with key observed NOEs between the C_6 ether and the C_{11} hydrogens as well as the C_9 alkene and the C_{17} hydrogens (Scheme 6). The stereochemical arrangement of **22** at C_{10} places the spirocyclic oxygen in a pseudoequatorial orientation in the half chair of the pyran ring. The transoidal spirocycle **22** appears to be the result of kinetic control under the described reaction conditions. While resubmission of the spirocycle **20** to acidic conditions (CSA, PhMe, 18 h) *did not* result in the formation of any of the transoidal (10*S*,13*R*) product **22**, treatment of transoidal spirocycle **22** to the identical conditions (CSA, PhMe) did lead to slow conversion toward the cisoidal product **20** with extended reaction times (40% conversion to **20**α by ^{1}H NMR after 24 h).[16] The kinetic preference for the transoidal orientation of the bisspirocycle **22** may be due to a minimization of the C–O dipoles present at C_{10} and C_{13} in the nonpolar solvent.[11,17] Further efforts to improve the ratio of the spirocycle **22** under alternate conditions (acidic or basic) and to access the natural transoidal spirocycle are under continued investigation.

4. Conclusion

The first successful example of the construction of the unprecedented transoidal (10*S*,13*R*) bisspirocycle in the azaspiracid ring system has been achieved. The synthesis of the transoidal bisspirocycle is facilitated by the novel use of a sulfone located in the C_{12} position. The apparent preference for the 10*S*,13*R*[13] transoidal orientation, as shown in **22**, over the alternate transoidal stereochemistry in the natural product **1**, may be worth further consideration. Construction of the C_{10} and C_{13} spirocyclic linkages in the absence of the C_{12} sulfone resulted in formation of the undesired cisoidal (10*R*,13*S*) stereochemistry. Finally, the efficient entry into the C_1–C_{19} carbon backbone of azaspiracid (**1**) has been achieved using a key Julia coupling strategy. Our progress toward the natural stereochemistry at C_{10} and C_{13} as well as the total synthesis of azaspiracid will be reported in due course.

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13. The C_{13} stereochemistry does represent the nonnatural isomer due to the priority ranking of the C_{12} sulfone.
14. For a recent review of bisspiroketals, see: Brimble, M. A.; Farés, F. A. *Tetrahedron* **1999**, *55*, 7661–7706.
15. Spiroketal **22**: To a stirred solution of **21** (13.0 mg, 0.0172 mmol) in PhMe (2.4 mL) at −78°C was added CSA (36 mg, 0.155 mmol). After 10 min, the reaction was allowed to warm to ambient temperature over a period of 35 min. After an additional 90 min, the reaction was quenched with solid $NaHCO_3$, diluted with 33% EtOAc/hexanes (10 mL), filtered through a small plug of SiO_2 (33% EtOAc/hexanes rinse) and concentrated in vacuo. The crude oil was purified by chromatography over silica gel, eluting with 5–40% EtOAc/hexanes, to give sequentially **20** (6.3 mg, 0.0083 mmol, 49%) and **22** (5.6 mg, 0.0074 mmol, 43%) as colorless oils. **22**: $[\alpha]_D^{23}$ −45.5° (*c* 0.43, $CHCl_3$); IR (neat) 3070, 2925, 2854, 1460, 1308 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.89 (dd, $J=2.0$, 8.0 Hz, 2H), 7.74–7.78 (m, 4H), 7.22–7.25 (m, 6H), 6.86–6.94 (m, 3H), 5.39–5.64 (m, 3H), 5.32 (d, $J=10.0$ Hz, 1H), 5.20 (dd, $J=4.0$, 5.6 Hz, 1H), 4.29 (dd, $J=6.6$, 12.5 Hz, 1H), 4.09 (dd, $J=2.0$, 5.0 Hz, 1H), 3.93–3.96 (m, 1H), 3.80–3.82 (m, 1H), 3.59 (t, $J=6.3$ Hz, 2H), 3.33 (s, 3H), 2.70 (dd, $J=12.2$, 12.5 Hz, 1H), 2.52 (dd, $J=6.5$, 12.2 Hz, 1H), 2.42–2.49 (m, 1H), 1.80–2.14 (m, 8H), 1.52–1.70 (m, 2H), 1.16 (s, 9H), 1.30 (d, $J=6.0$ Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6); δ 140.9, 136.4, 134.7, 133.6, 131.8, 131.2, 130.4, 130.2, 129.9, 129.3, 128.9, 128.2, 108.1, 105.8, 103.1, 75.6, 73.6, 73.1, 65.9, 63.9, 55.8, 41.5, 38.4, 32.7, 29.2, 28.9, 27.5, 23.5, 19.9, 16.0, 14.8; HRMS (FAB+) calcd. for $C_{43}H_{54}O_8SSiLi$ (M+Li) 765.3469, found 765.3466.
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