



## Studies toward the total synthesis of YW3699, a sesterterpenoid GPI biosynthesis inhibitor: preparation of the tri-substituted cyclooctene ring using the RCM reaction

Reiko Mizutani, Katsuyuki Nakashima, Yoshinori Saito, Masakazu Sono, Motoo Tori\*

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan

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### ABSTRACT

The preparation of eight-membered carbocycles with tri-substituted double bonds has been attempted using RCM reactions. One of the stereoisomers subjected to the RCM reaction provided a desired compound which will be used for the synthesis of YW3699.

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YW3699 (**1**)<sup>1</sup> is a fungal metabolite isolated in 1998 by Wang et al. (Fig. 1) and was shown to inhibit the biosynthesis of glycosylphosphatidylinositol (GPI) in tripanosoma.<sup>2,3</sup> It has a unique carbon skeleton, namely four consecutive five-, eight-, six-, and five-membered rings, with an ester of C9 hydroxycarboxylic acid. The absolute configuration is yet to be established. We have been studying the preparation of carbocycles with tri-substituted cycloheptenes using the ring-closing metathesis (RCM) reaction.<sup>4</sup> Our next challenge was the preparation of eight-membered carbocycles by the RCM reaction. Recently more than ten papers<sup>5–13</sup> describing the application of RCM reactions to the synthesis of eight-membered substances have been reported. However, the construction of the eight-membered carbocycles especially having a tri-substituted double bond is still a challenging task in the synthetic work. Syntheses of cyclooctenes are attempted by carefully planning the precursors. Here we report our preliminary results on the applications of the RCM reactions to the construction of the eight-membered carbocycles.

The strategy for the total synthesis of YW3699 (**1**) is to construct the ring D as well as to introduce the oxygen function of the ring A at the last step.<sup>14</sup> Thus, the target molecule is the simple tri-cyclic substance like compound **6**. We would like to know the feasibility of the cyclization to the tri-substituted eight-membered carbocycle. Therefore, we have planned to test the RCM reactions of the four diastereoisomers with the epoxide ring. The trans relationship of the eight- and six-membered rings in rings B and C was realized by the conjugate addition to compound **2**. The epoxide ring was introduced to a five-membered enone as illustrated in Scheme 1.

The 1,4-addition of *i*-PrOSiMe<sub>2</sub>CH<sub>2</sub>MgCl in the presence of CuBr-Me<sub>2</sub>S and the Tamao reaction<sup>15</sup> to enone **2**<sup>16</sup> afforded **7**, as the sole isomer with trans stereochemistry (Scheme 2). The stereo-

chemistry was established based on 2D NMR spectra. Protection of the primary alcohol as a TBDPS ether, ketalization using the

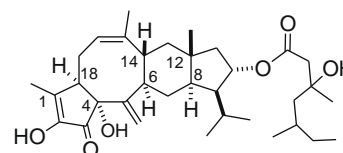
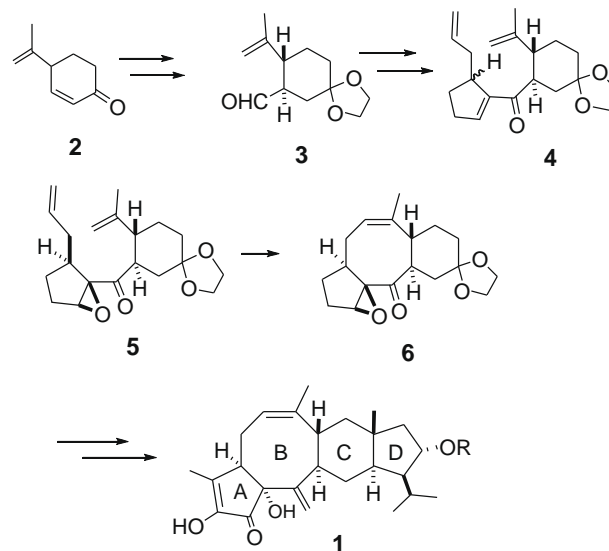


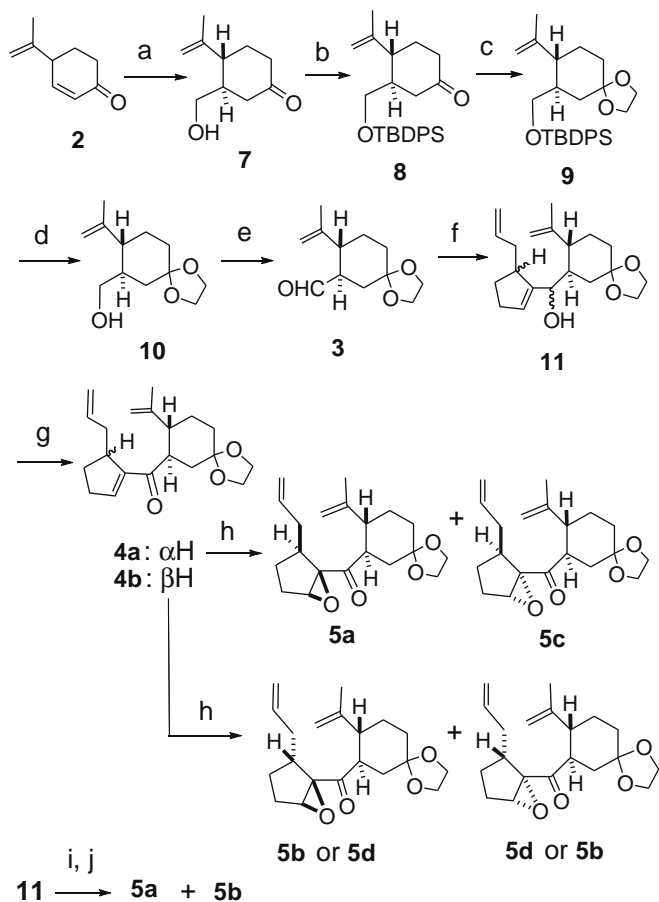
Figure 1. Structure of YW3699 (**1**).



Scheme 1. Synthetic plan.

\* Corresponding author. Tel.: +81 88 602 8462; fax: +81 88 655 3051.

E-mail address: [tori@ph.bunri-u.ac.jp](mailto:tori@ph.bunri-u.ac.jp) (M. Tori).

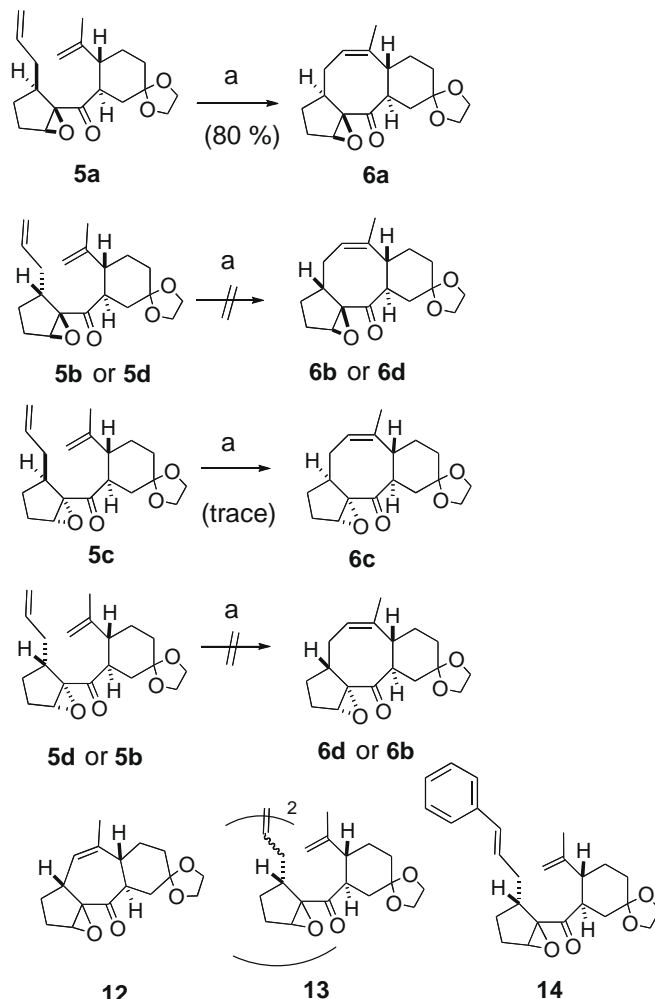


**Scheme 2.** Reagents and conditions: (a) *i*-PrOSiMe<sub>2</sub>CH<sub>2</sub>Cl, Mg, CuBr–Me<sub>2</sub>S, THF; then KF, KHCO<sub>3</sub>, H<sub>2</sub>O<sub>2</sub>, 86%; (b) TBDPSCI, NEt<sub>3</sub>, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 93%; (c) TMS-OCH<sub>2</sub>CH<sub>2</sub>OTMS, TMSOTf, CH<sub>2</sub>Cl<sub>2</sub>, 70%; (d) TBAF, THF, 76%; (e) Dess–Martin Oxid., 99%; (f) trisylhydrazone of 2-allylcyclopentanone, *t*-BuLi, THF, 90%; (g) Dess–Martin Oxid., **4a** (46%), **4b** (37%); (h) H<sub>2</sub>O<sub>2</sub>, NaOH; (i) *t*-BuOOH, VO(acac)<sub>2</sub>; (j) Dess–Martin Oxid., **5a** (28%), **5b** (22%).

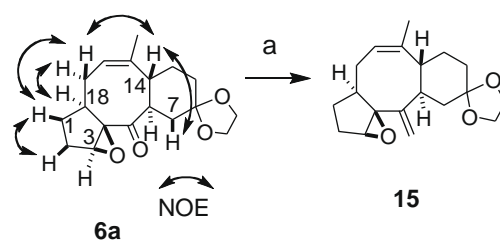
Tsunoda and Noyori method,<sup>17</sup> deprotection of the silyl ether (TBAF), and Dess–Martin periodinane oxidation<sup>18</sup> gave aldehyde **3**. The trisyl hydrazone of 2-allylcyclopentanone was treated with *t*-BuLi<sup>19</sup> and was reacted with **3** to produce alcohol **11** as a mixture of diastereoisomers with a 90% yield.<sup>20</sup> The mixture of alcohols **11** was oxidized (Dess–Martin) into separable enones **4a** and **4b** and gave yields of 46 and 37%, respectively. Enone **4a** was converted (H<sub>2</sub>O<sub>2</sub>, NaOH) into epoxides **5a**<sup>21</sup> and **5c**<sup>22</sup> with yields of 67% and 13%, respectively. Enone **4b** was also converted into epoxides **5b** and **5d** with yields of 65% and 18%, respectively; however, the configuration was not determined at this stage. Alternatively, alcohol **11** was converted into epoxides under Sharpless epoxidation conditions<sup>23</sup> followed by oxidation, to generate two diastereoisomeric epoxides, **5a** and **5b**, with yields of 28% and 22%, respectively. The configurations were later assigned by the analysis of the cyclized compound **6a**.

Each epoxide was treated with Grubbs II (30 mol %)<sup>24</sup> in CH<sub>2</sub>Cl<sub>2</sub> (1 mM) under reflux for 10 h (Scheme 3). The diene **5a** efficiently afforded the tri-carbocyclic ketone **6a**<sup>25</sup> with an 80% yield as the sole product. The structure of **6a** was solved by X-ray crystallographic<sup>26</sup> and 2D NMR spectral analysis. The 3D structure is shown in Figures 2 and 3.

From **5c**, cyclized product **6c** was obtained only in trace amounts. However, epoxide **5b** (or **5d**) provided a ring-contracted seven-membered compound **12**,<sup>27–29</sup> dimeric at the terminal vinyl group **13**<sup>29</sup> and the styrene adduct **14**.<sup>29</sup> Epoxide **5d** (or **5b**)



**Scheme 3.** Reagents and conditions: (a) Grubbs II (30 mol %), CH<sub>2</sub>Cl<sub>2</sub> (0.5 mol %), reflux, 10 h.



**Figure 2.** The selected NOESY correlations of **6a** and methylenation. (a) Tebbe reagent, THF, 85%.

afforded many products without recovery of the starting material, which could not be analyzed due to the minute amounts. The product **6a** had the desired configurations for the synthesis of YW3699 (**1**). Compound **6a** was further efficiently converted to **15**<sup>30</sup> with Tebbe reagent (85%) (Fig. 2).<sup>31</sup> We then carried out the RCM reactions of compounds **4a** and **4b** to compare the effect of the epoxide ring and the double bond at the 3,4-positions. However, the starting material was recovered.

In summary, we have reported the synthetic efforts toward the sesterterpenoid YW3699 (**1**). The RCM reaction was successfully applied to the construction of the tri-substituted cyclooctene ring. Interestingly, only one diastereoisomer was efficiently cyclized to the corresponding tri-cyclic compound. This result confirms the

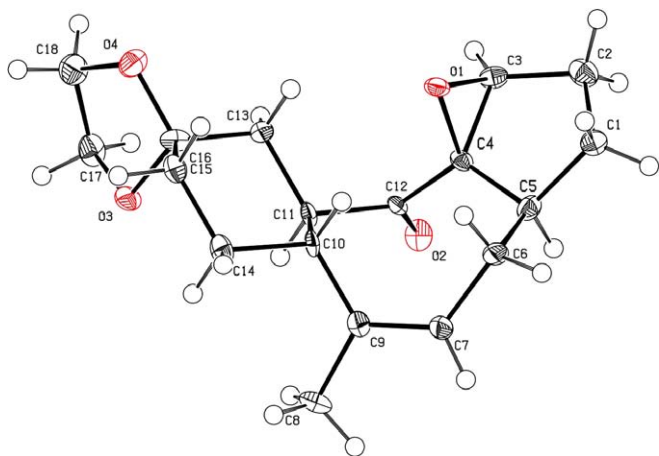


Figure 3. The 3D structure of compound **6a** analyzed by X-ray crystallography.

importance of the conformation of the diene substrate. Namely, only one of the four possible diastereoisomers, **5a–d**, had the suitable geometry for cyclization. The total synthesis of YW3699 (**1**) is currently under progress in this line.

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- After oxidation of the diastereoisomers, the ratio was 1:1 due to the isomers at the C-18, based on the  $^{13}\text{C}$  NMR data.
- Compound 5a**: FTIR 1700  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.70 (1H, m), 5.01 (1H, m), 4.96 (1H, m), 4.77 (1H, s), 4.71 (1H, m), 3.96 (4H, m), 3.75 (1H, s), 3.08 (1H, ddd,  $J = 12.6, 11.1, 3.6$  Hz), 2.47 (1H, m), 2.37 (1H, m), 2.02–1.95 (2H, m), 1.83–1.75 (3H, m), 1.72 (3H, s), 1.66 (2H, m), 1.57–1.44 (5H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  207.8 (C), 146.9 (C), 136.5 (CH), 116.5 ( $\text{CH}_2$ ), 111.4 ( $\text{CH}_2$ ), 108.2 (C), 69.0 (C), 64.4 ( $\text{CH}_2 \times 2$ ), 62.5 (CH), 46.0 (CH), 45.3 (CH), 38.5 ( $\text{CH}_2$ ), 37.9 (CH), 34.3 ( $\text{CH}_2$ ), 34.1 ( $\text{CH}_2$ ), 28.8 ( $\text{CH}_2$ ), 25.9 ( $\text{CH}_2$ ), 23.3 ( $\text{CH}_2$ ), 20.3 ( $\text{CH}_3$ ); MS (CI)  $m/z$  333 [ $\text{M}+\text{H}$ ] $^+$ , 315, 209 (base), 181, 165, 99, 86; HRMS (CI). Found  $m/z$  333.2065 [ $\text{M}+\text{H}$ ] $^+$ ,  $\text{C}_{20}\text{H}_{29}\text{O}_4$  requires 333.2066.
- Compound 5c**: FTIR 1700  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.74 (1H, ddt,  $J = 17.1, 9.9, 7.2$  Hz), 5.00 (1H, br d,  $J = 17.1$  Hz), 4.95 (1H, br d,  $J = 9.9$  Hz), 4.69 (1H, m), 4.63 (1H, br s), 3.98 (4H, m), 3.59 (1H, s), 2.97 (1H, ddd,  $J = 12.3, 11.4, 3.3$  Hz), 2.72 (1H, m), 2.36 (1H, dt,  $J = 11.4, 3.3$  Hz), 2.25 (1H, m), 2.04 (3H, m), 1.81–1.74 (3H, s), 1.71 (3H, s), 1.69–1.53 (3H, m), 1.26 (1H, d,  $J = 12.6$  Hz), 1.08 (1H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  208.4 (C), 148.6 (C), 136.5 (CH), 115.9 ( $\text{CH}_2$ ), 110.1 ( $\text{CH}_2$ ), 108.0 (C), 71.5 (C), 64.4 ( $\text{CH}_2 \times 2$ ), 63.6 (CH), 46.3 (CH), 43.3 (CH), 38.1 ( $\text{CH}_2$ ), 36.6 ( $\text{CH}_2$ ), 34.8 ( $\text{CH}_2$ ), 34.4 ( $\text{CH}_2$ ), 29.2 ( $\text{CH}_2$ ), 27.3 ( $\text{CH}_2$ ), 25.3 ( $\text{CH}_2$ ), 22.1 ( $\text{CH}_3$ ); MS (CI)  $m/z$  333 [ $\text{M}+\text{H}$ ] $^+$  (base), 315, 209, 181, 99, 61; HRMS (CI). Found  $m/z$  333.2057 [ $\text{M}+\text{H}$ ] $^+$ ,  $\text{C}_{20}\text{H}_{29}\text{O}_4$  requires 333.2066.
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- Compound 6a**: mp 110–111  $^\circ\text{C}$  (from hexane); IR 1700, 1612  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  5.47 (1H, td,  $J = 9.0, 1.2$  Hz, H-16), 3.95–3.90 (4H, m, ketal), 3.41 (1H, s, H-3), 3.36 (1H, td,  $J = 13.2, 3.6$  Hz, H-14), 2.68 (1H, ddd,  $J = 13.2, 12.9, 4.1$  Hz, H-6), 2.44 (1H, ddd,  $J = 13.1, 9.0, 9.0$  Hz, H-17b), 2.33 (1H, t,  $J = 12.9$  Hz, H-7 $\beta$ ), 2.26 (1H, m, H-18), 2.00 (1H, dd,  $J = 14.3, 8.1$  Hz, H-2), 1.93 (1H, ddd,  $J = 13.1, 9.0, 2.9$  Hz, H-17 $\alpha$ ), 1.80 (1H, m), 1.79 (1H, m), 1.77 (1H, m), 1.74 (1H, m), 1.68 (1H, m), 1.67 (1H, m), 1.66 (1H, m), 1.63 (3H, s, H-25), 1.11 (1H, m, H-1);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  208.9 (C-5), 140.4 (C-15), 124.8 (C-16), 107.5 (C-8), 72.7 (C-4), 64.3 (ketal X 2), 63.6 (C-3), 55.4 (C-6), 44.8 (C-18), 36.3 (C-14), 34.6 (C-7), 34.3 (C-12), 28.1 (C-17), 27.7 (C-2), 26.3 (C-1), 25.8 (C-13), 19.1 ( $\text{CH}_3$ ); HRMS obs.  $m/z$  304.1673 Calcd for  $\text{C}_{18}\text{H}_{24}\text{O}_4$  304.1675; MS (CI)  $m/z$  305 [ $\text{M}+\text{H}$ ] $^+$ , 304 [ $\text{M}$ ] $^+$  (base), 287, 243, 164, 99.
- X-ray crystallographic analysis of compound **6a**: All diagrams and calculations were performed using maXus (Bruker Nonius, Delft & MacScience, Japan). Mo  $K\alpha$  radiation,  $\lambda = 0.71073$  Å, 8445 measured reflections, 8613 independent reflections, 6935 observed reflections, Data collection: DIP Image plate, Program(s) used to refine structure: SHELXL-97 (Sheldrick, 1997); refinement on  $F^2$ , full matrix least squares refinement. Crystal data: monoclinic, Cc,  $a = 20.554(2)$  Å,  $b = 7.1676(7)$  Å,  $c = 21.723(2)$  Å,  $\alpha = 90^\circ$ ,  $\beta = 103.206(2)^\circ$ ,  $\gamma = 90^\circ$ ,  $V = 3115.7(6)$  Å $^3$ ,  $R$  (all) = 0.0390,  $R$  (gt) = 0.0371. Crystallographic data for compound **6a** have been deposited at the Cambridge Crystallographic Data Center as supplementary publication number CCDC 707740. Copies of the data can be obtained, free of charge, via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by mailing to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk)).
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- Compound 12**:  $\delta$  5.29 (1H, br d,  $J = 5.1$  Hz), 1.73 (3H, s); HRMS (CI) Found  $m/z$  291.1579 [ $\text{M}+\text{H}$ ] $^+$ ,  $\text{C}_{17}\text{H}_{23}\text{O}_4$  requires 291.1597. **13**:  $\delta$  5.30 (1H, t,  $J = 4.4$  Hz), 4.71 (1H, m), 4.65 (1H, s), 1.69 (3H, s). **14**:  $\delta$  7.33–7.19 (5H, m), 6.37 (1H, d,  $J = 15.6$  Hz), 6.10 (1H, dt,  $J = 15.6, 7.5$  Hz), 4.73 (1H, m), 4.69 (1H, m), 1.71 (3H, s).
- Compound 15**: FTIR 1630  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.44 (1H, t,  $J = 8.7$  Hz), 4.92 (1H, d,  $J = 1.2$  Hz), 4.83 (1H, d,  $J = 1.8$  Hz), 3.94 (4H, m), 3.12 (1H, br s), 2.91 (1H, br t,  $J = 11.1$  Hz), 2.47 (1H, ddd,  $J = 12.9, 11.7, 3.9$  Hz), 2.37 (1H, m), 2.29 (1H, t,  $J = 12.9$  Hz), 1.99–1.53 (10H, m), 1.61 (3H, s), 1.09 (1H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  149.4 (C), 140.2 (C), 124.0 (CH), 114.0 ( $\text{CH}_2$ ), 108.8 (C), 70.6 (C), 65.4 (CH), 64.3 ( $\text{CH}_2$ ), 64.1 ( $\text{CH}_2$ ), 48.2 (CH), 47.8 (CH), 40.7 ( $\text{CH}_2$ ), 38.4 (CH), 34.2 ( $\text{CH}_2$ ), 28.1 ( $\text{CH}_2$ ), 27.3 ( $\text{CH}_2$ ), 27.1 ( $\text{CH}_2$ ), 26.5 ( $\text{CH}_2$ ), 19.0 ( $\text{CH}_3$ ); MS (CI)  $m/z$  303 [ $\text{M}+\text{H}$ ] $^+$  (base), 302, 285, 241, 99; HRMS (CI) Found  $m/z$  303.1953 [ $\text{M}+\text{H}$ ] $^+$ ,  $\text{C}_{19}\text{H}_{27}\text{O}_3$  requires 303.1960.
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