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SYNTHETIC STUDIES TOWARD ANTITUMOR SESQUITERPENOID QUADRONE

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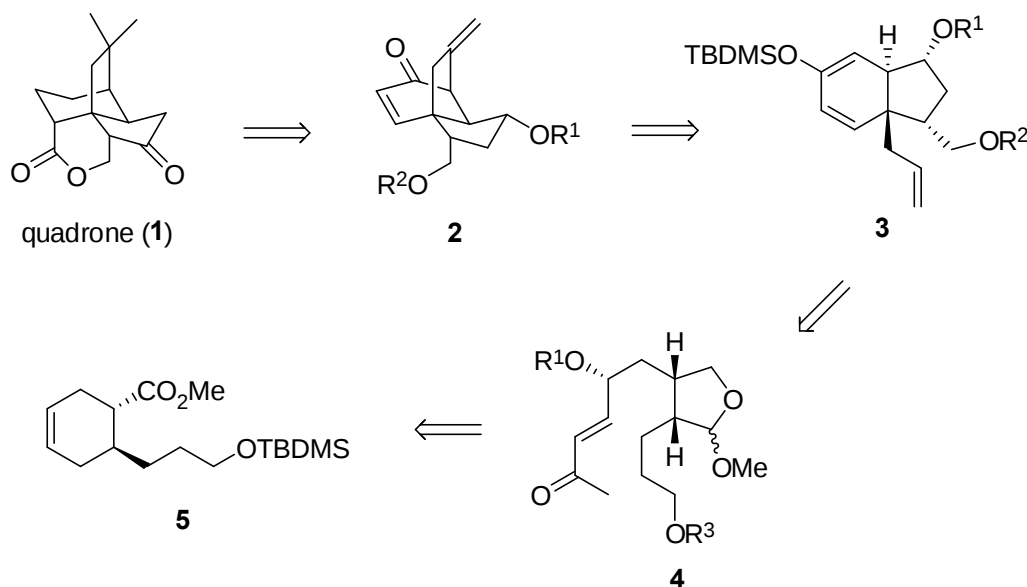
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#Dedicated to Professor Emeritus Akira Suzuki on the occasion of his 80th birthday.

Abstract – A palladium-catalyzed cycloalkenylation and an acid-promoted intramolecular Michael reaction were utilized as the key steps in a synthetic approach to sesquiterpene quadrone **1**. This route capitalizes upon the ability of the above reactions to stereoselectively assemble tricyclic core **15** of quadrone **1**.

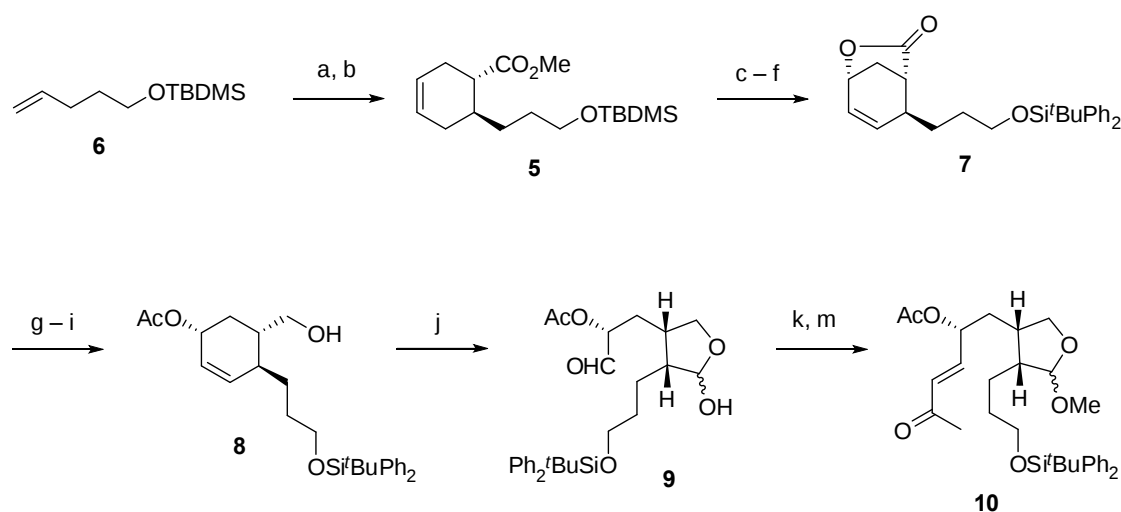
Due to the challenging molecular architecture and antitumor activity of sesquiterpene quadrone **1**, it has been an interest to synthetic organic chemists, and various approaches to **1** have been reported.¹ We first became interested in **1** during our studies on whether our palladium-catalyzed cycloalkenylation² could effectively construct highly strained tricyclic core **2**, which is found in **1**. As shown in **Scheme 1**, we envisaged our retrosynthesis of **1** as follows: palladium-catalyzed cycloalkenylation of silyl enol ether **3** could provide tricyclic compound **2**, which could be converted into **1** by functional group manipulations. Compound **3** could be synthesized from acetal **4** via an acid-promoted intramolecular Michael reaction.³ Finally, substrate **4** could be prepared from cyclohexene **5**, which could be constructed by an intermolecular Diels–Alder reaction of 1,3-butadiene and (*E*)-methyl 6-*tert*-butyldimethylsiloxyhex-2-enoate.

Olefin metathesis between olefin **6** and methyl acrylate in the presence of Grubbs second generation



Scheme 1. Retrosynthetic Analysis of the Tricyclic Core of Quadrone (1)

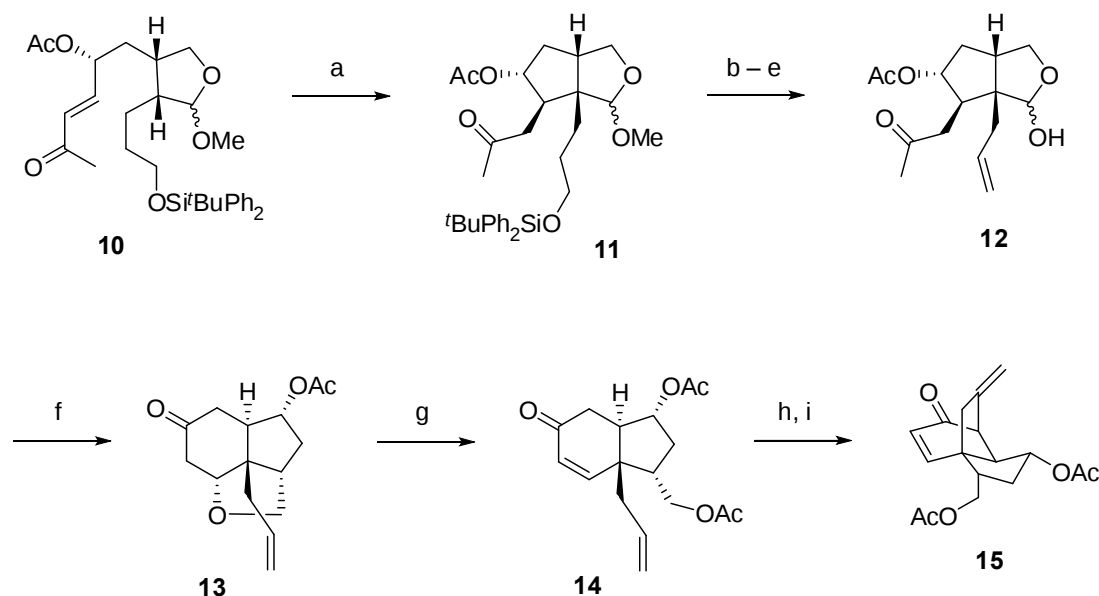
catalyst afforded (*E*)-methyl 6-*tert*-butyldimethylsiloxyhex-2-enoate in 78% yield, which was subsequently subjected to an intermolecular Diels–Alder reaction with 1,3-butadiene to give rise to cyclohexene derivative **5** (88%). Hydrolysis of **5** was accompanied by deprotection of the hydroxyl group to provide the corresponding hydroxyl acid, which was then transformed into unsaturated lactone **7**⁴ through iodolactonization followed by elimination. Reduction of **7** with DIBALH (1 equiv.) furnished the corresponding hydroxyl aldehyde, which was treated with acetic anhydride. The resulting aldehyde was reduced with NaBH₄ to give alcohol **8**. Ozonolysis of **8** and subsequent reductive treatment produced aldehyde **9**,



Scheme 2. Reagents and conditions: (a) methyl acrylate, Grubbs catalyst (0.05 mol %), reflux, 78%; (b) 1,3-butadiene, hydroquinone, toluene, 220 °C, 88%; (c) LiOH, 1,4-dioxane–H₂O, reflux, 91%; (d) I₂, KI, NaHCO₃, CH₂Cl₂–H₂O; (e) ^tBuPh₂SiCl, imidazole, DMF; (f) DBU, THF, reflux, 70% for 3 steps; (g) DIBAL-H, CH₂Cl₂, –78 °C, (h) Ac₂O, DMAP, CH₂Cl₂; (i) NaBH₄, MeOH, 67% for 3 steps; (j) O₃, MeOH then Me₂S, –78 °C, 96%; (k) Ph₃P=CHCOMe, MeCN, reflux, 83%; (m) PPTS, CH(OMe)₃, CH₂Cl₂, 90%.

which was converted into requisite unsaturated ketone **10** for the first key reaction *via* Wittig reaction followed by acetalization (**Scheme 2**).

Then **10** was treated with a catalytic amount of TfOH. As expected, the intramolecular Michael reaction proceeded stereoselectively to give oxabicyclo[3.3.0]octane compound **11** in 97% yield, which was transformed into hemiacetal **12** by deprotection of the hydroxyl group followed by dehydration⁵ and hydrolysis. An intramolecular aldol reaction of **12** in the presence of pyrrolidine was accompanied by an intramolecular Michael reaction to afford keto ether **13**. To obtain the desired *trans*-hydrindane derivative for the second key reaction, **13** was subjected to a retro Michael reaction under acidic conditions. After acetylation of the corresponding diol, enone diacetate **14**⁴ was isolated in 96% yield. Compound **14** was transformed into the corresponding silyl enol ether, and the subsequent palladium-catalyzed cycloalkenylation successfully synthesized desired cyclization product **15**⁴ in 89% yield (**Scheme 3**).



Scheme 3. Reagents and conditions: (a) TfOH (0.5 mol %), CH₂Cl₂, 97%; (b) Bu₄NF, THF; (c) *o*-NO₂PhSeCN, Bu₃P, THF, 65% for 2 steps; (d) NaIO₄, MeOH-H₂O, 76%; (e) 10% HCl, acetone, 80%; (f) pyrrolidine, benzene, reflux, 72%; (g) TsOH, Ac₂O, benzene, reflux, 96%; (h) TBDMSOTf, Et₃N, CH₂Cl₂; (i) Pd(OAc)₂ (20 mol %), DMSO, O₂ (1 atm), 89% for 2 steps.

The relative stereochemistry was established using NOE experiments employing cyclization product **15** as shown in **Figure 1**.

In conclusion, we demonstrated that **15**, a potential intermediate in the synthesis of **1**, could be stereoselectively constructed by combining a palladium-catalyzed cycloalkenylation with an acid-catalyzed intramolecular Michael reaction.

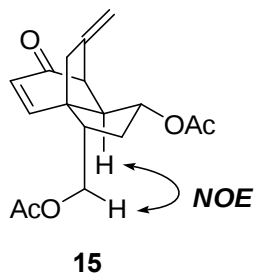


Figure 1. NOE Experiment of Cyclization Product 15.

ACKNOWLEDGMENT

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REFERENCES

1. Isolation: G. J. Calton, R. L. Ranieri, and M. A. Espenshade, *J. Antibiot.*, 1978, **31**, 38. Recent syntheses of quadrone: (a) A. B. Smith, III, J. P. Konopelski, B. A. Wexler, and P. A. Sprengeler, *J. Am. Chem. Soc.*, 1991, **113**, 3533; (b) C. G. Sowell, R. L. Wolin, and R. D. Little, *Tetrahedron Lett.*, 1990, **31**, 485; (c) A. P. Neary and P. J. Parsons, *J. C. Soc., Chem. Commun.*, 1989, 1090; (d) P. Magnus, L. M. Principe, and M. J. Slater, *J. Org. Chem.*, 1987, **52**, 1483; (e) R. L. Funk and M. M. Abelman, *J. Org. Chem.*, 1986, **51**, 3247.
2. M. Toyota, T. Wada, K. Fukumoto, and M. Ihara, *J. Am. Chem. Soc.*, 1998, **120**, 4916. Selected applications to natural product synthesis: (a) M. Toyota, T. Asano, and M. Ihara, *Org. Lett.*, 2005, **7**, 3929; (b) M. Toyota, M. Sasaki, and M. Ihara, *Org. Lett.*, 2003, **5**, 1193; (c) M. Toyota, T. Odashima, T. Wada, and M. Ihara, *J. Am. Chem. Soc.*, 2000, **122**, 9036; (d) M. Toyota, T. Wada, and M. Ihara, *J. Org. Chem.*, 2000, **65**, 4565.
3. G. Stork and K. S. Atwal, *Tetrahedron Lett.*, 1983, **24**, 3819. Selected applications to natural product synthesis: (a) M. Toyota, Y. Nishikawa, K. Motoki, N. Yoshida, and K. Fukumoto, *Tetrahedron*, 1993, **49**, 11189; (b) M. Toyota, Y. Nishikawa, K. Motoki, N. Yoshida, and K. Fukumoto, *Tetrahedron Lett.*, 1993, **34**, 6099.
4. Satisfactory analytical data were obtained for all new compounds. Compound 7: IR (neat) 1771 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ 7.64 (4H, dd, *J*=8.0 and 1.5 Hz), 7.45-7.35 (6H, m), 6.21-6.15 (1H, m), 5.75-5.70 (1H, m), 4.73 (1H, dd, *J*=5.3 and 5.3 Hz), 3.68 (2H, td, *J*=5.9 and 1.5 Hz), 2.74-2.71 (1H, m), 2.51-2.45 (1H, m), 2.31 (1H, ddd, *J*=11.3, 5.3 and 5.3 Hz), 2.09 (1H, d, *J*=11.3 Hz), 1.67-1.50 (4H, m) and 1.05 (9H, s). ¹³C NMR (CDCl₃, 100 MHz) δ 179.2, 135.3, 134.5, 133.6, 129.5, 128.5, 127.5,

73.7, 63.4, 42.2, 38.3, 31.2, 30.5, 29.4, 27.0, and 19.3. LRMS m/z 363 ($M^+ - C_4H_9$). Anal. Calcd for $C_{26}H_{32}O_3Si$: C, 74.24; H, 7.67. Found: C, 74.39; H, 7.56. Compound **14**: IR (neat) 1738, 1732, and 1682 cm^{-1} . 1H NMR ($CDCl_3$, 400 MHz) δ 7.20 (1H, δ , $J=10.1$ Hz), 6.00 (1H, d, $J=10.1$ Hz), 5.74 (1H, dddd, $J=17.1$, 9.5, 8.7, and 6.5 Hz), 5.19 (1H, d, $J=9.5$ Hz), 5.12 (1H, dd, $J=17.1$ and 1.2 Hz), 5.04-4.97 (1H, m), 4.06 (1H, dd, $J=11.4$ and 7.4 Hz), 3.99 (1H, dd, $J=11.4$ and 6.8 Hz), 2.70 (1H, ddd, $J=15.1$, 9.0, and 9.0 Hz), 2.64-2.48 (4H, m), 2.34 (1H, dd, $J=13.4$ and 6.5 Hz), 2.09 (1H, dd, $J=13.4$ and 8.7 Hz), 2.07 (3H, s), 2.06 (3H, s), 1.43 (1H, ddd, $J=15.1$, 5.7 and 3.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.0, 170.7, 170.4, 154.1, 132.3, 130.2, 119.7, 74.8, 66.0, 47.4, 46.5, 40.3, 40.1, 36.5, 33.8, 21.1, and 21.0. LRMS m/z 265 ($M^+ - C_3H_5$). HRMS calcd for $C_{14}H_{17}O_5$ ($M^+ - C_3H_5$) 265.1076. Found: 265.1070. Compound **15**: IR (neat) 1738, 1732, and 1682 cm^{-1} . 1H NMR (C_6D_6 , 600 MHz) δ 6.60 (1H, d, $J=9.6$ Hz), 5.71 (1H, dd, $J=9.6$ and 1.5 Hz), 5.31-5.29 (1H, m), 4.84 (1H, s), 4.68 (1H, ddd, $J=9.0$, 9.0 and 6.6 Hz), 3.86 (1H, s), 3.84 (1H, dd, $J=11.4$ and 6.0 Hz), 3.70 (1H, dd, $J=11.4$ and 6.0 Hz), 2.37 (1H, ddd, $J=15.0$, 9.0, and 9.0 Hz), 2.34 (1H, d, $J=9.0$ Hz), 1.89 (1H, d, $J=17.0$ Hz), 1.77-1.72 (1H, m), 1.64 (1H, ddd, $J=17.0$, 2.4, and 2.4 Hz), 1.59 (3H, s), 1.58 (3H, s), and 1.38 (1H, ddd, $J=15.0$, 6.6, and 4.2 Hz). ^{13}C NMR (C_6D_6 , 150 MHz) δ 196.2, 170.0, 169.8, 152.7, 143.2, 128.3, 114.2, 75.3, 65.7, 63.6, 59.4, 53.5, 42.0, 40.2, 35.4, 20.4, and 20.3. LRMS m/z 304 (M^+). Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.05; H, 6.77.

5. (a) K. B. Sharpless and M. W. Young, [*J. Org. Chem.*, 1975, **40**, 947](#); (b) P. A. Grieco, S. Gilman, and M. Nishizawa, [*J. Org. Chem.*, 1976, **41**, 1485](#).