Convenient Synthesis of Angular Triquinane from 4-Alkenylfulvene via Thermal Cycloaddition Followed by Skeletal Rearrangement of the Resulting [4 + 2] Adduct

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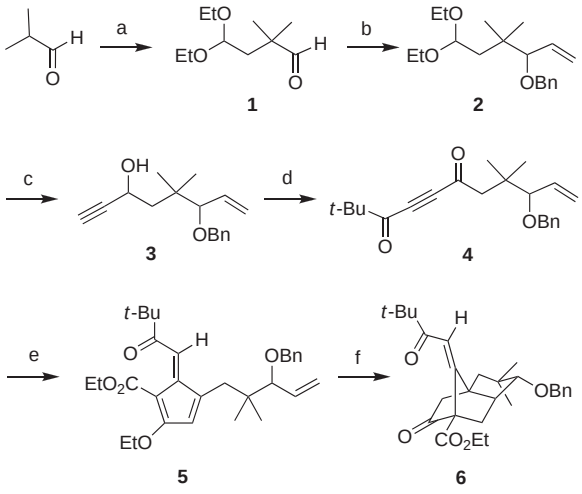
Alkenylfulvene prepared by the annulation of allylidenetriphenylphosphorane with 1,4-ynedione proceeded thermal cycloaddition in a highly regio- and stereoselective manner to give [4 + 2] adduct which was then converted into triquinane derivative by the treatment with LHMDS-*t*-BuOK after hydrolysis of the enol ether group.

Cycloaddition reaction of fulvene is attractive tool to construct various fused ring-systems. Unique 6π electrons of fulvene allow reacting with dienophiles, 1,3-dipolarophiles and dienes to produce [4 + 2], [6 + 2], and [6 + 4] cycloaddition products and competition among these cycloadditions has been observed in many cases.[1] Although intramolecular cycloaddition of 4-alkenylfulvenes has advantage to control the competition,[2] the approach is limited by difficulty of regioselective preparation of substituted fulvenes.[3] We have reported that 4-alkenylfulvene could be prepared regioselectively by the reaction of allylidenetriphenylphosphorane with 1,4-ynedione and underwent thermal [4 + 2] cycloaddition in a highly regio- and diastereoselective manner.[4] The resulting adduct was transformed into the bicyclo[3.3.0]octene derivative which possessed proper functionalities to provide an access to triquinane skeleton as found in pentalenic acid and pentalenolactone.[5] Thus, we set out to study an access to the triquinanes using this methodology since they have been still attractive synthetic target of organic chemists in terms of their unique structural feature and biological activities. We now disclose that regioselective synthesis and subsequent thermal cycloaddition of 4-alkenylfulvene provides a good yield of [4 + 2] adduct which is then converted into angular triquinane via unexpected skeletal rearrangement.

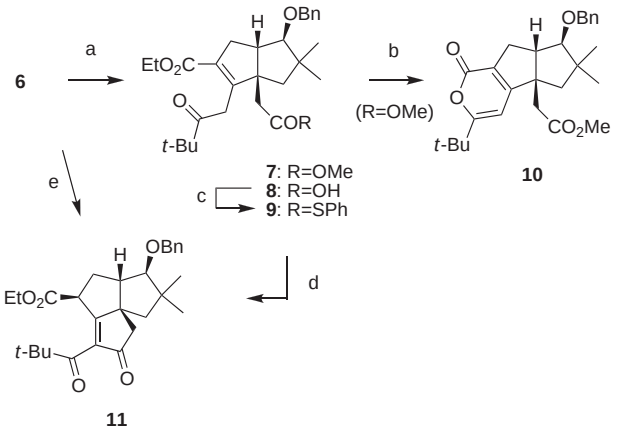
The present investigation commenced by synthesis of *t*-butyl-substituted ynedione **4** (Scheme 1) because previous synthesis from the corresponding phenyl-substituted ynedione led to the formation of a mixture of E/Z isomers (1:2.5) in which Z isomer proceeded [4 + 2] cycloaddition while E isomer gave poor results.[4b] We expected that the bulky *t*-butyl substituent would retard *E*-fulvene formation due to steric repulsion with the 4-substituent. The monoacetal **1** prepared from 2-methylpropanal was treated with vinylmagnesium bromide followed by benzyl bromide to give **2**. Hydrolysis of **2** and ethynylation of the resulting aldehyde gave **3** which was then converted into *t*-butyl-substituted 1,4-ynedione **4** via a sequence consisted of protection, the Sonogashira reaction, and then the Jones oxidation. Reaction of the 1,4-ynedione with 2-ethoxyallylidenetriphenylphosphorane proceeded nicely at 0 °C to give almost exclusively the *Z*-fulvene **5** in 94% yield as expected. Thermal cycloaddition of the fulvene **5** in refluxing toluene followed by mild acid hydrolysis of the resulting [4 + 2] adduct gave the tricyclic ketone **6**[6] stereoselectively.



Scheme 1. Reagents and conditions; (a) (i) $C_6H_{11}NH_2$, CH_2Cl_2, rt, 79%, (ii) $(EtO)_2CHCH_2Br$, LDA, HMPA, THF, −78 °C, then tartaric acid, H_2O, 0 °C, 96%. (b) (i) vinylmagnesium bromide, THF, 0 °C, 94%, (ii) BnBr, NaH, TBAI, THF 30 °C, 91%. (c) (i) TsOH, acetone, H_2O, 96%, (ii) ethynylmagnesium bromide, THF, 0 °C, 80%. (d) (i) TMSCl, Et_3N, ether, rt, (ii) *t*-BuCOCl, $(PPh_3)_2PdCl_2$, CuI, Et_3N, benzene, rt, (iii) citric acid, MeOH, H_2O, rt, 81% (from **3**), (iv) Jone's reagent, rt, 83%. (e) $Ph_3P{=}CHC(OEt){=}CHCO_2Et$, THF, 0 °C, 24 h, 94%. (f) (i) toluene, 100 °C, 85%, (ii) TFA, THF, H_2O, rt, 1 h, 72%.

Having achieved efficient formation of the tricyclic ketone **6** using *t*-butyl 1,4-ynedione **4**, conversion of **6** into triquinane skeleton was next investigated (Scheme 2). Treatment of **6** with NaOMe in MeOH proceeded ring opening even at −78 °C to give the methyl ester **7** in 79% yield. When the reaction was carried out at −10 °C, the pyrone **10** was generated in 71% yield. Similarly, treatment of **7** with LDA in THF also gave **10** in 41% yield and in both cases the expected formation of triquinane by cyclization between the α position of ketone and the bridgehead methyl ester was not observed. The cyclization was achieved with more reactive phenylthioester **9**, which was prepared from **6** by the treatment with DBU in aqueous THF and then condensation of the resulting acid **8** with benzenethiol. Treatment of **9** with LDA in THF gave triquinane **11** but in a low yield (28%).

Finally, we found that the desired triquinane **11** was formed directly from the ketone **6**. When the ketone **6** was treated with LHDMS in the presence of potassium *t*-butoxide in THF at −78 °C, skeletal transformation occurred to give **11**.[7] The reaction underwent only under the above conditions using the combination of LHDMS and potassium *t*-butoxide and in the

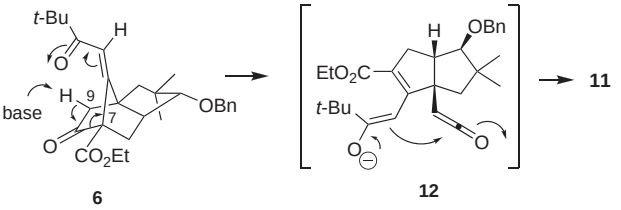


Scheme 2. Reagents and conditions; (a) for preparation of **7**: NaOMe, MeOH, THF, −78 °C, 79%; for the preparation of **8**: DBU, THF, H_2O, rt, 94%. (b) NaOMe, MeOH, THF, −10 °C, 1 h, 71% (from **6**). (c) DCC, PhSH, 92%. (d) LDA, THF, −78 °C, 28%. (e) LHDMS, *t*-BuOK, THF, −10 °C, 4 h, 72%.

Table 1. Reaction conditions of skeletal rearrangement[a]

Entry	Base	Additive (mol amt.)	Yield[b] of **11**/%
1	LHMDS	—	0
2	LHMDS	LiCl (1.0)	0[c]
3	LHMDS	*t*-BuOK (1.0)	42
4	LHMDS	*t*-BuOK (1.5)	72
5	LHMDS	*t*-BuOK (3.0)	0
6	*s*-BuLi	*t*-BuOK (1.5)	0

[a]All reaction were carried out at −78 °C in THF using 1.1 mol amt. of base. [b]Isolated yield. [c]The acid **8** was obtained in 61% yield.



Scheme 3. A possible mechanism of skeletal rearrangement.

absence of potassium *t*-butoxide no formation of **11** was observed (Table 1). The best yield (72%) was obtained in the presence of 1.5 molar amounts of potassium *t*-butoxide. The structure of **11** was confirmed by a combination of COSY and HMBC spectra in the NMR experiments. Thus, the skeletal transformation may be explained in terms of easiness of the C7–C8 bond cleavage addressed to release of ring strain and existence of the two electron-withdrawing groups at the 7 and 10 positions. Deprotonation at the 9 position of **6** affects the C7–C8 bond cleavage to generate the ketene **12** (Scheme 3). Recyclization of **12** and successful double bond migration gives rise **11** which has stable β-oriented ethoxycarbonyl group.

In summary, stereoselective synthesis of triquinane skeleton was achieved via thermal intramolecular [4 + 2] cycloaddition of 4-alkenylfulvenes followed by skeletal rearrangement.

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6 Data for **6**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27–7.35 (m, 5H), 6.38 (s, 1H), 4.54 (s, 2H), 4.36–4.25 (m, 2H × 1/2), 4.10–3.99 (m, 2H × 1/2), 3.25 (d, J = 9.17 Hz, 2H) 2.48 (dd, J = 21.6 Hz, J = 17.2 Hz, 2H), 2.36 (t, J = 4.49 Hz, 1H), 2.31 (t, J = 4.49 Hz, 1H), 2.24–2.15 (m, 1H), 1.91 (d, J = 14.7 Hz, 1H), 1.70 (d, J = 14.8 Hz, 1H), 1.25 (t, J = 7.15 Hz, 3H), 1.18 (s, 3H), 1.16 (s, 9H), 1.09 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.24, 205.30, 167.72, 159.48, 138.81, 127.65, 127.26, 112.64, 92.10, 73.01, 69.35, 61.12, 52.40, 49.22, 43.82, 43.73, 38.30, 31.59, 29.65, 26.44, 25.33, 14.19, HRMS (TOF) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{36}O_5Na$ 475.2460; Found 475.2447.

7 Data for **11**: mp 146–147 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.29 (m, 5H), 4.62 (dd, J = 15.0, 11.9 Hz, 2H), 4.13 (bq, J = 7.0 Hz, 2H), 3.65 (dd, J = 12.2, 7.9 Hz, 2H), 3.33 (d, J = 6.4 Hz, 1H), 2.79 (d, J = 16.5 Hz, 1H), 2.62 (d, J = 16.5 Hz, 1H), 2.47 (bt, J = 7 Hz, 1H), 2.34–2.27 (m, 1H), 2.21–2.17 (m, 1H), 1.66 (d, J = 13.4 Hz, 1H), 1.45 (d, J = 13.4 Hz, 1H), 1.30 (bt, J = 7.0 Hz, 3H), 1.19 (s, 9H), 1.12 (s, 3H), 1.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.69, 204.258, 185.86, 170.92, 138.46, 137.65, 128.41, 127.65, 127.21, 95.07, 72.61, 61.38, 56.05, 54.51, 51.9, 50.27, 44.39, 43.99, 43.60, 37.62, 37.62, 31.57, 27.10, 25.81, 22.64, 21.01, 14.05; ν_{max} (neat): 1734, 1706, 1669, 1623 cm^{-1}; HRMS (TOF) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{36}O_5Na$ 475.2460, found 475.2448.

Published on the web (Advance View) March 15, 2008; doi:10.1246/cl.2008.454