4-Acetoxy- and 4-Triflyloxy-2,6,6-trimethyl-2,4-cyclohexadienones as Nondimerizing Alternatives to 2,6,6-Trimethyl-2,4-cyclohexadienone. Efficient Synthesis of Several Bicyclo[2.2.2]octenone Derivatives

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Abstract: 4-Acetoxy- and 4-triflyloxy-2,6,6-trimethyl-2,4-cyclohexadienones were employed as non-dimerizing alternatives to 2,6,6-trimethyl-2,4-cyclohexadienone in Diels-Alder reactions with substituted acetylenes which facilitated the synthesis of substituted bicyclo[2.2.2]octen-2,5-diones, bicyclo[2.2.2]octadienones and 5methylenebicyclo[2.2.2]octen-2-ones.

Key words: 2,4-cyclohexadienones, Diels-Alder reactions, vinyl triflates, bicyclo[2.2.2]octendiones, bicyclo[2.2.2]octadienones

During our studies on competitive photochemical rearrangements of bicyclo[2.2.2]octenone derivatives, a need for the synthesis of substituted bicyclo[2.2.2]octen-2,6diones 1, bicyclo[2.2.2]octadienones 2 and 5-methylenebicyclo[2.2.2]oct-7-en-2-ones 3 (Figure 1) has arisen. While there are no efficient general methods available for the preparation of bicyclo[2.2.2]oct-7-en-2,5-diones¹ which are immediate precursors of 5-methylenebicyclo[2.2.2]oct-7-en-2-ones, there exist reports on synthesis of bicyclo[2.2.2]octadienones via Diels-Alder reactions of 2,4-cyclohexadienones and acetylene derivatives.² In principle, it should be possible to prepare bicyclo[2.2.2]octadienones of the required type 2 via Diels-Alder reactions of appropriate acetylene derivatives with 2,6,6-trimethyl-2,4-cyclohexadienone (4). However, the tedious procedures involved in the preparation of 4 and its high propensity to dimerize have deterred us from using



this approach.³ It is pertinent to mention that despite the difficulties involved in the preparation and handling of 4, it has been used in the total synthesis of natural products on a number of occassions.⁴

During the search for an alternative to **4**, 4-acetoxy-2,6,6-trimethyl-2,4-cyclohexadienone (**5**) prepared by Soukup *et al.*,⁵ attracted our attention. Interestingly, although **5** is quite stable and accessible in large quantities its Diels-Alder chemistry has not been studied.^{6,7} We herein report the first use of 4-acetoxy-2,6,6-trimethyl-2,4-cyclohexadienone (**5**) and 4-triflyloxy-2,6,6-trimethyl-2,4-cyclohexadienone (**6**) as attractive alternatives to **4** in Diels-Alder reactions with substituted acetylenes and a novel approach to title compounds **1-3** starting from readily available 4-ketoisophorone (**7**) (Schemes 1-3).



Scheme 1

Compound 5 was prepared from 7 following the procedure developed by Soukup et al.⁵ The Diels-Alder reactions of 5 with substituted acetylenes such as ethyl propiolate (8a), dimethyl acetylenedicarboxylate (8b), phenylacetylene (8c) and diphenylacetylene (8d) were performed by heating 5 with two equivalents of an acetylene derivative at an appropriate temperature to obtain the adducts **9a-d** in excellent yields (Scheme 1).⁸ The regioselectivity observed in the reactions of 5 with 7a and 7c is noteworthy. Subsequent hydrolysis of 9a-d with potassium carbonate in ethanol or methanol at 0 °C proceeded smoothly to furnish the desired bicyclo[2.2.2]octendiones 1a-d in >93% yields.9 It should be mentioned that compounds of type **1** were prepared by others from hydroquinone and maleic anhydride in very low yields (16%).¹

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After several unsuccessful attempts to convert **1a** into **2a**. it was finally decided to adopt Cacchi's procedure¹⁰ for the conversion of enolizable ketones into olefins. Accordingly, **1a-d** were converted into corresponding vinyl triflates 10a-d in >90% yield by treating 1a-d with LHMDS in THF at -78 °C and then with N-phenyltriflimide. Vinyl triflates 10a-d were then subjected to Cacchi's conditions (HCOOH, n-Bu₃N, Pd(PPh₃)₂Cl₂, DMF, 60-80 °C) to obtain the desired bicyclo[2.2.2]octadienones 2a-d in good overall yields (Scheme 2). However, a rethinking enlightened us with the idea that instead of starting with 5, the cyclohexadienone 6 could be employed to obtain the compounds 10a-d directly rather than in three steps. This hypothesis was immediately examined. The cyclohexadienone 6 was prepared from 4-ketoisophorone in >90%yield using the conditions employed for the conversion of **1a-d** into **10a-d**. Diels-Alder reactions of **6** with acetylenes 8a-d proceeded smoothly as expected to provide the adducts 10a-d in excellent yield.8 However, in the case of 8a, regioisomer 10e (12%) was also produced along with 10a (73%).





Scheme 2

Towards synthesis of 5-methylenebicyclo[2.2.2]oct-7-en-2-ones **3a-d**, compounds **1a-d** were treated with triphenylmethylenephosphorane in toluene at 60-80 °C. While **1a, 1c** and **1d** underwent smooth and selective Wittig olefination at the less hindered keto group, in the case of **1b** the ester group interfered and the major product was **11** (37%). The desired compound **3b** was obtained only in 25% yield (Scheme 3). The structures of all the new compounds were unambiguously established by their IR, ¹H and ¹³C NMR, DEPT and low- and high-resolution mass spectral data.





It is important to note that compounds **1a-d** with an active methylene group and two distinguishable keto groups should allow further transformations characteristic to these groups. Similarly, compounds **2a-d** with a vinyl triflate moiety should undergo facile Heck-type and Stille coupling reactions. In fact this transformation forms the corner stone of a common approach to quinane-based and cedranoid natural products being developed in our laboratory. Nevertheless, compounds **1** and **2** clearly hold substantial potential.

In conclusion, the present studies unravelled two new stable 2,4-cyclohexadienones as well as attractive and stable alternatives to highly useful but readily dimerizing and tedious to prepare 2,6,6-trimethyl-2,4-cyclohexadienone (4). In fact, both 5 (200 mM) and 6 (50 mM) can be prepared in large scale. The targeted compounds 1-3 were obtained in good overall yields by the present procedures and hence an efficient route for these types of compounds has been developed. Studies on competetive di- π -methane and oxa-di- π -methane rearrangements¹¹ of compounds 1-3 are in progress in our laboratory and the details will be published in the near future.

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- (8) General procedure for Diels-Alder reactions of 5 and 6 with acetylene derivatives 8a-d. A mixture of 5/6 (5 mM) and 8 (10 mM) were heated for 24 h (at 80 °C for 8a,b and 120 °C for 8c,d). Removal of excess 8 under reduced pressure followed by column chromatography of the crude adduct on silica gel using 15% ethyl acetate in hexanes as eluent furnished the desired adducts 9a-d and 10a-e.

Spectral data of compound **9a**. IR (film): 3080, 2966, 1775, 1765, 1721, 1645 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.42 (d, *J* = 7.0 Hz, 1H), 5.70 (d, *J* = 2.8 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.38 (dd, *J* = 7.0, 2.8 Hz, 1H), 2.14 (s, 3H), 1.62 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.16 (s, 3H), 1.03 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 208.4, 167.8, 164.0, 156.0, 146.0, 137.4, 115.2, 60.6, 56.1, 52.0, 40.1, 27.5, 26.1, 21.0, 15.0, 14.0. EIMS (70 eV): m/z (relative intensity) 292 (M⁺, 1), 251(11), 223 (13), 180 (14), 177 (13), 135 (28), 70 (100).

HRMS (EI): Calcd for $C_{16}H_{20}O_5~(M^+)$ 292.1311, found 292.1310. Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.96. Found: C, 65.84; H, 6.93.

Spectral data of compound **10a**. IR (film): 2980, 1727, 1653 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.44 (d, *J* = 6.6 Hz, 1H), 5.87 (d, *J* = 3.1 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.57 (dd, *J* = 6.6, 3.1 Hz, 1H), 1.70 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.25 (s, 3H), 1.12 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 206.7, 163.5, 154.7, 144.9, 137.5, 119.8, 118.4, 61.0, 57.2, 51.9, 39.9, 27.5, 26.6, 15.0, 14.0. FABMS: m/z (relative intensity) 383 (M⁺+1, 61), 337 (49), 267 (32), 159 (19), 137 (21), 91 (22), 70 (100). HRMS (FAB): Calcd for C₁₅H₁₈O₆F₃S (M⁺+1) 383.0776, found 383.0775.

(9) General procedure for hydrolysis of compounds 9a-d. A solution of an enol-actate 9 (2 mM) in 20 mL of ethanol (for 9a) or methanol (for 9b-d) was cooled to 0 °C. Then K₂CO₃ (1 mM) was added and stirring was continued until the completion of hydrolysis as indicated by TLC analysis (75 min for 9a and 10 min for 9b-d). Then the alcohol was removed under reduced pressure and the residue was diluted with ethyl acetate. Washed the contents with water and dried the organic layer over anhyd. Na₂SO₄. Removal of solvent followed by column chromato-grapy of thus obtained residue on silica gel using 25% ethyl acetate in hexanes as eluent furnished the products 1a-d.

Spectral data of compound **1a**. IR (film): 2970, 1728, 1710, 1705, 1630 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.26 (d, *J* = 7.0 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.30 (d, *J* = 7.0 Hz, 1H), 2.36 (d, *J* = 19.2 Hz, 1H), 2.18 (d, *J* = 19.2 Hz, 1H), 1.51 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.16 (s, 3H), 1.13 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 211.7, 205.9, 163.5, 140.0, 136.9, 62.1, 61.1, 51.7, 42.3, 42.0, 26.2, 25.3, 15.7, 14.0. EIMS (70 eV): m/z (relative intensity) 250 (M⁺, 31), 205 (22), 181 (19), 121 (21), 109 (21), 107 (21), 91 (26) 70 (100). HRMS (EI): Calcd for C₁₄H₁₈O₄ (M⁺) 250.1205, found 250.1205.

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