

Spiro Compounds

Beyond the Dimer and Trimer: Tetraspiro[2.1.2⁵.1.2⁹.1.2¹³.1³]hexadecane-1,3,5,7-tetraone—the Cyclic Tetramer of CarbonylcyclopropaneKseniya N. Sedenkova,^[a, b] Elena B. Averina,^{*,[a, b]} Yuri K. Grishin,^[a] Kristian S. Andriasov,^[a] Svetlana A. Stepanova,^[a] Vitaly A. Roznyatovsky,^[a] Andrei G. Kutateladze,^{*,[c]} Victor B. Rybakov,^[a] Dmitry V. Albov,^[a] Tamara S. Kuznetsova,^[a] and Nikolay S. Zefirov^[a]

Abstract: Tetraspiro[2.1.2⁵.1.2⁹.1.2¹³.1³]hexadecane-1,3,5,7-tetraone **4**, a unique tetraketone containing a cyclooctane core and four spiroannulated cyclopropane moieties, represents the previously unknown cyclotetramer of carbonylcyclopropane. For this purpose oxidation of the parent polyspirocyclic hydrocarbon was examined under various oxidative conditions, and the reactivity of oxidants towards methylene groups of the eight-membered cycle, activated by adjacent spirocyclopropane rings, was evaluated and contrasted. Whereas the treatment of tetraspirohexadecane with ozone resulted in monooxidation, its reaction with methyl(trifluoromethyl)dioxirane afforded the product of four-fold oxidation, triketoalcohol **10**. Subsequent oxidation of the latter with Dess–Martin periodinane gave the target tetraketone **4**.

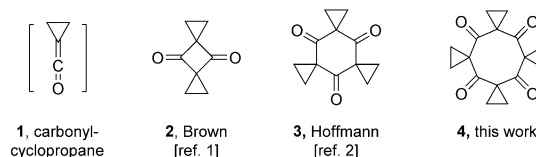


Figure 1. Cyclooligomers of carbonylcyclopropane 1.

ring, which allows for an effective carbonyl conjugation with the cyclopropyl moiety.

Hoffmann's synthesis of the trimer **3** was based on an interrupted oligomerization. Conceivably for entropic reasons, the tetramer (**4**) of carbonyl cyclopropane was not obtained, so we set out to develop an alternative approach for the synthesis of this fascinating tetraketone by a direct oxidation of the parent hydrocarbon **5**.

Direct oxidation of methylene groups has attracted growing attention in the context of new synthetic method developments.^[3] In particular, cyclopropane derivatives represent advantageous substrates for such oxidative processes because the three-membered ring, not unlike the π -systems, activates the adjacent CH₂ groups toward the oxygenation.^[4–8] Oxidizing agents, such as ozone on silica gel,^[4] CrO₃ in various conditions,^[5] in situ generated RuO₄,^[6] dioxiranes,^[7] H₂O₂ in the presence of Fe- or Ti-based catalysts^[3b, 8] have been employed for the selective conversion of activated α -methylene groups in cyclopropanes into the carbonyl function. It is instructive to mention that the resulting cyclopropane, conjugated with a carbonyl group, represents a versatile building block for the assembly of polyspirocyclopropanes.^[9] Nevertheless, in most of the described cases the oxidation of methylene C–H bonds afforded the products of one-fold oxygenation. To the best of our knowledge, very few examples of a diketone-producing two-fold oxidation of hydrocarbons containing three-membered rings were reported.^[4a,b, 5a]

In the present work, we report our findings on the oxidation of polyspirocyclic hydrocarbon **5** (Figure 2), containing four spirocyclopropane rings, with several oxidizing agents. Our goal was to develop a general methodology of exhaustive methylenes oxidation of **5** in order to access tetraketone **4**, an appealing precursor for [8]-rotane and [8]-heterorotanes.

Hydrocarbon **5** was obtained by a recently developed synthesis, starting from readily available adamantane-1,3-dicarbox-

In 1975 Brown demonstrated that carbonylcyclopropane **1**,^[1] obtained by flash vapor thermolysis (FVT) of spiroannulated Meldrum acid, dimerizes into dispiro[2.1.2.1]octane-4,8-dione **2** (Figure 1), which is the first member of cyclooligomers of ketene **1**. However, trimer **3** was not formed by a simple cyclotrimerization during the FVT, which prompted its synthesis by organozinc chemistry by Hoffmann^[2a] who declared it “structurally fascinating and of preparative interest” in addition to being “aesthetically pleasing.”^[2b] The trimer **3** indeed has unusual structural features, such as a nearly planar cyclohexane

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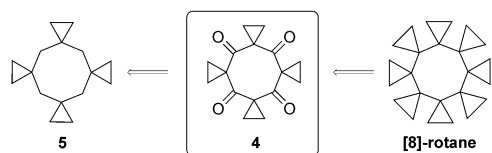
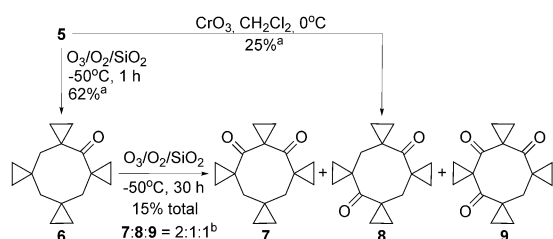


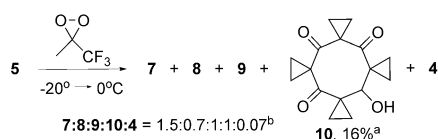
Figure 2. Polyspirocyclopropane structures built on cyclooctane core.

ylic acid, in 30% yield over six steps.^[10] The oxidation of **5** on silica gel with ozone (1 h exposure) afforded monoketone **6** as the sole product (Scheme 1). The subsequent oxidation of **6** with extended exposure to ozone for 30 h was accompanied by complete conversion of the starting ketone into the mixture of 1,3-diketone **7**, 1,5-diketone **8**, and 1,3,5-triketone **9** in the ratio of 2:1:1, respectively (Scheme 1). Yet, significant decomposition of the organic material did not allow for continued exhaustive oxidation. An alternative procedure^[4b] of cycling the temperature (seven cycles, 0.5–1 h each) afforded the mixture of ketones **6–8** in total yield of 59% (**6**:**7**:**8** = 1:0.8:0.8). The reaction of **5** with 20-fold excess of CrO₃ afforded mainly 1,5-diketone **8** with only 3% of 1,3-diketone **7** forming under these conditions (Scheme 1). Increasing the excess of oxidizing agent did not afford the products of further oxidation. Also, no reaction was observed with the complex CrO₃-3,5-dimethylpyrazole.^[5b]



Scheme 1. Oxidation of tetracyclopropane **5** under the treatment with ozone or CrO₃. [a] Isolated yield. [b] Estimated by ¹H NMR spectra.

Methyl(trifluoromethyl)dioxirane (TFDO) has been described as a powerful agent for oxidation of hydrocarbons.^[11] In contrast to the literature examples,^[7] the oxidation of **5** with 12-fold excess TFDO did not stop at the monooxidation (afforded no monoketone **6**). The reaction of the substrate activated by four cyclopropane fragments proceeded smoothly, leading to the products of multiple oxidation (Scheme 2). When the reaction was carried out for two hours at $-20 \rightarrow 0^\circ\text{C}$, the mixture

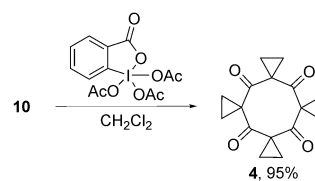


Scheme 2. Oxidation of spirocyclic hydrocarbon **5** under the treatment with TFDO. [a] Isolated yield. [b] Estimated by ¹H NMR spectra.

of 1,3- and 1,5-diketones was obtained (**7**:**8** = 1:1.5). The use of 8-fold excess of TFDO per methylene group at the same temperature and longer reaction time, up to 20 h, led to further oxidation. Di- and triketones **7–9** were isolated from the reaction mixture, as well as triketoalcohol **10**, which is the product of a 4-fold oxidation. The target tetraketone **4** was also observed in the spectra of the reaction mixture, albeit as a minor product (Scheme 2).

Alcohol **10** was isolated and its further oxidation was optimized. Neither Swern conditions^[12] nor the treatment with pyridinium chlorochromate (PCC) afforded tetraketone **4**. Yet, the treatment of alcohol **10** with the reactive Dess–Martin periodinane^[13] led to complete conversion of the starting compound into the target tetraketone **4** (Scheme 3). The obtained novel carbonyl and polycarbonyl compounds **4–8** and **10** were isolated and characterized by HRMS, ¹H and ¹³C NMR. The structures of diketones **7** and **8** and target tetraketone **4** were also confirmed by X-ray crystallographic analysis (Figure 3).^[14]

As shown in the X-ray structure (Figure 3c and 3d), each carbonyl group in tetraketone **4** assumes the *cis*-bisecting conformation to one of its three-membered ring neighbors, providing the most effective conjugation of the π -acceptor



Scheme 3. Synthesis of the target tetraketone **4** under Dess–Martin conditions.

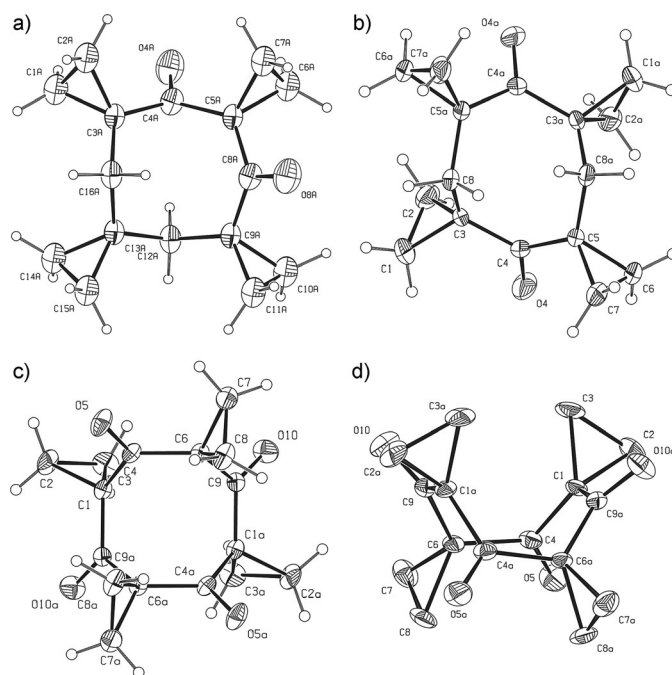


Figure 3. ORTEP^[15] drawing of the molecular structures of diketones: a) **7**, b) **8**, and c) and d) tetraketone **4**.

substituent and cyclopropane,^[16] whereas the conjugation with the second adjacent ring is disrupted by twisting. We have determined the experimental kinetic parameters for the cyclooctane ring inversion in **4**: $\Delta H^\ddagger = 7.3 \pm 0.2 \text{ kcal mol}^{-1}$, $\Delta S^\ddagger = -14.5 \pm 0.9 \text{ cal mol}^{-1} \text{ K}^{-1}$, $\Delta G^\ddagger_{298} = 10.5 \pm 0.2 \text{ kcal mol}^{-1}$ (see the Supporting Information for details).

A DFT study of the structure of tetraketone **4** identified the lowest energy S_4 -symmetric tub-conformer (Figure 4a and 4b), which is in full agreement with the obtained X-ray structure shown in Figure 3c. This main conformer is reminiscent of the cyclooctatetraene's tub-conformer, and the similarity is not en-

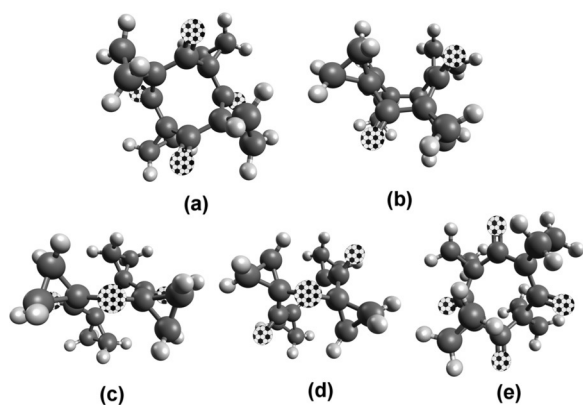


Figure 4. DFT structures, B3LYP/6-311 + G(d,p). Main S_4 -symmetric conformer of **4** (top): view down the improper rotation axis (a); side view (b). C_2 -symmetric transition state for ring inversion in **4** (Bottom): views up and down the two-fold axis (c) and (d); side view (e).

tirely superfluous. The flattening of the cyclohexane ring to the near D_{3h} symmetry in the trispirotriketone described by Hoffmann^[2] was attributed to conjugation, which permits each carbonyl to adopt the favoured *cis*-bisected conformation with respect to both adjacent cyclopropane rings. Such flattening in the eight-membered ring is not possible, as it would require the eight CCC bond angles in the cyclooctane moiety to reach the value of 135° . As a result, the molecule adopts the tub conformation with alternating conjugated and unconjugated carbonylcyclopropane moieties, reminiscent of the alternating single and double bonds in cyclooctatetraene.

The ring inversion occurs by rotation about one of the unconjugated C–C bonds through a C_2 -symmetric transition state shown in Figure 4c–e, in which one of the carbonyls necessarily becomes conjugated to its both cyclopropyl neighbors. The first view down the C_2 axis (Figure 4c) shows this CO group, which is dissecting cyclopropyls on both sides. As a trade-off, the opposite C_2 -aligned carbonyl (Figure 4d) is not dissecting either one of its cyclopropyl neighbors. The B3LYP/6-311 + G(d,p) ZPE-corrected activation barrier for this ring inversion is calculated to be $11.4 \text{ kcal mol}^{-1}$, which is in good agreement with the experimental free activation energy of $10.5 \text{ kcal mol}^{-1}$.

All four protons belonging to the CH_2CH_2 moiety in each cyclopropyl unit are magnetically not equivalent in the S_4 -symmetric molecule of **4**. At ambient temperature, the average ex-

perimental ^{13}C – ^1H SSCs matched well the RFF DU8c-computed values (experimental: 2.5 Hz; calcd: 2.6 Hz).^[17] Upon lowering the temperature to -85°C , the sole singlet in the ^1H NMR split into two multiplets (Figure 5), although we were unable to completely freeze out the ring inversion process. However, using the six calculated proton–proton coupling constants, we were able to simulate the low temperature spectrum with empirically adjusted chemical shifts (gray line in Figure 5, also see the Supporting Information for details).

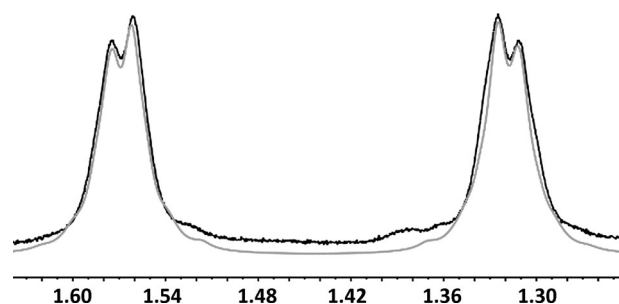


Figure 5. Low temperature (-85°C) ^1H NMR spectrum of **4** (black line) and its simulation (gray line) using computed proton spin–spin coupling constants and empirically adjusted chemical shift differences.

In summary, due to the activation of methylene groups by adjacent spirocyclopropane fragments, hydrocarbon **5** is amenable to multiple oxygenations with excess oxidant. Chromium (VI) oxide was found to be the most selective in multiple oxidations, whereas TFDO demonstrated the highest reactivity. Such oxidation patterns may be related to the nature of oxidants; although the reaction with CrO_3 , which presumably proceeds via carbocationic intermediates,^[5b] is sensitive to the electronic factors, the oxidation by strong radical oxidants (O_3 or TFDO) is more tolerant to the accumulation of multiple carbonyl functions in the molecule. The combination of contemporary highly effective oxidizing agents allows for the exhaustive four-fold oxidation of the hydrocarbon **5** and offers ready access to the unique non-enolizable tetraketone **4**—an attractive compound from both theoretical and preparative standpoint. Moreover, the synthesis of **4** comes exactly three decades after the trimer of carbonylcyclopropane, which was synthesized by Hoffmann and co-workers.

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- [1] G. J. Baxter, R. F. C. Brown, F. W. Eastwood, K. J. Harrington, *Tetrahedron Lett.* **1975**, *16*, 4283. The original name *carbonylcyclopropane* has been used for compound **1** in the present article; IUPAC name for compound **1** is *cyclopropylidenemethanone*.
- [2] a) H. M. R. Hoffmann, A. Walenta, U. Eggert, D. Schomburg, *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 607–608; *Angew. Chem.* **1985**, *97*, 599–600; b) H. M. R. Hoffmann, U. Eggert, A. Walenta, E. Weineck, *J. Org. Chem.* **1989**, *54*, 6096–6100.
- [3] For examples, see: a) T. Newhouse, P. S. Baran, *Angew. Chem. Int. Ed.* **2011**, *50*, 3362–3374; *Angew. Chem.* **2011**, *123*, 3422–3435; b) M. S. Chen, M. C. White, *Science* **2010**, *327*, 566–571; c) S. Das, C. D. Incarvito, R. H. Crabtree, G. W. Brudvig, *Science* **2006**, *312*, 1941–1943.
- [4] a) E. Proksch, A. de Meijere, *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 761–762; *Angew. Chem.* **1976**, *88*, 802–803; b) E. Proksch, A. de Meijere, *Tetrahedron Lett.* **1976**, *17*, 4851–4854; c) D. Kaufmann, H.-H. Fick, O. Schallner, W. Spielmann, L.-U. Meyer, P. Göllitz, A. de Meijere, *Chem. Ber.* **1983**, *116*, 587–609; d) M. Zarth, A. de Meijere, *Chem. Ber.* **1985**, *118*, 2429–2449; e) J. P. Kutney, Y.-H. Chen, S. J. Rettig, *Can. J. Chem.* **1996**, *74*, 666–676; f) P. Müller, M. Rey, *Helv. Chim. Acta* **1982**, *65*, 1191–1196; g) H. Fuhrer, A. K. Ganguly, K. W. Gopinath, T. R. Govindachari, K. Nagaranjan, B. R. Pai, P. C. Parthasarathy, *Tetrahedron* **1970**, *26*, 2371–2390.
- [5] a) M. A. Hashem, P. Weyerstahl, *Synthesis* **1983**, 583–585; b) M. G. Banwell, N. Haddad, J. A. Huglin, M. F. MacKay, M. E. Reum, J. H. Ryana, K. A. Turner, *J. Chem. Soc. Chem. Commun.* **1993**, 954–957; c) A. V. Nizovtsev, M. S. Baird, I. G. Bolesov, *Tetrahedron* **2004**, *60*, 3717–3729; d) J. F. Toccanne, R. G. Bergmann, *Tetrahedron* **1972**, *28*, 373–387; e) Md. A. Hashem, P. Weyerstahl, *Tetrahedron* **1981**, *37*, 2473–2476; f) L. J. Stuart, J. P. Buck, A. E. Tremblay, P. H. Buist, *Org. Lett.* **2006**, *8*, 79–81; g) J. W. Palko, P. H. Buist, J. M. Manthorpe, *Tetrahedron: Asymmetry* **2013**, *24*, 165–168.
- [6] a) T. Hasegawa, H. Niwa, K. Yamada, *Chem. Lett.* **1985**, 1385–1386; b) L. Fitjer, B. Rissoma, A. Kanschika, E. Egert, *Tetrahedron* **1994**, *50*, 10879–10892; c) J. L. Coudret, S. Zöllner, B. J. Ravoo, L. Malara, C. Hanisch, K. Dörre, A. de Meijere, B. Waegell, *Tetrahedron Lett.* **1996**, *37*, 2425–2428;
- d) D. S. Teager, R. K. Murray Jr., *J. Org. Chem.* **1993**, *58*, 5548–5550; e) H. J. M. Gijzen, J. B. P. A. Wijnberg, C. van Ravenswaay, A. de Groom, *Tetrahedron* **1994**, *50*, 4733–4744; f) T. Kawai, T. Ooi, T. Kusumi, *Chem. Pharm. Bull.* **2003**, *51*, 291–294.
- [7] a) L. D'Accolti, A. Dinoi, C. Fusco, A. Russo, R. Curci, *J. Org. Chem.* **2003**, *68*, 7806–7810; b) E. Volker Dehmlow, N. Heiligenstädt, *Tetrahedron Lett.* **1996**, *37*, 5363–5364.
- [8] a) D. H. R. Barton, P. E. Eaton, W.-G. Liu, *Tetrahedron Lett.* **1991**, *32*, 6263–6264; b) C. B. Khouw, C. B. Dartt, J. A. Labinger, M. E. Davis, *J. Catal.* **1994**, *149*, 195–205.
- [9] a) A. de Meijere, S. I. Kozhushkov, *Chem. Rev.* **2000**, *100*, 93–142; b) A. de Meijere, S. I. Kozhushkov, H. Schill, *Chem. Rev.* **2006**, *106*, 4926–4996.
- [10] E. B. Averina, K. N. Sedenkova, S. G. Bakhtin, Yu. K. Grishin, A. G. Kutateladze, V. A. Roznyatovsky, V. B. Rybakov, G. M. Butov, T. S. Kuznetsova, N. S. Zefirov, *J. Org. Chem.* **2014**, *79*, 8163–8170.
- [11] R. Curci, L. D'Accolti, C. Fusco, *Acc. Chem. Res.* **2006**, *39*, 1–9 and references therein.
- [12] K. Omura, D. Swern, *Tetrahedron* **1978**, *34*, 1651–1660.
- [13] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
- [14] CCDC 1442055 (**4**), 1437891 (**7**), and 1429783 (**8**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.
- [15] L. J. Farrugia, *J. Appl. Crystallogr.* **1997**, *30*, 565–566.
- [16] a) F. H. Allen, *Acta Crystallogr. Sect. A* **1980**, *36*, 81–96; b) R. Hoffmann, R. B. Davidson, *J. Am. Chem. Soc.* **1971**, *93*, 5699–5705.
- [17] Relativistic Force Field: a) DU8c: A. G. Kutateladze, O. M. Mukhina, *J. Org. Chem.* **2015**, *80*, 10838–10848; b) DU8: A. G. Kutateladze, O. A. Mukhina, *J. Org. Chem.* **2015**, *80*, 5218–5225; c) DU4: A. G. Kutateladze, O. A. Mukhina, *J. Org. Chem.* **2014**, *79*, 8397–8406.

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