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Stereoselective one-pot preparation of 1,2,4,5-tetraalkylidene- and 1,4-dialkylidenecyclohexanes

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1,2,4,5-Tetraalkylidene- and 1,4-dialkylidenecyclohexanes were prepared by the regio- and stereoselective homo-coupling of skip-type diynes and enynes, and their Diels–Alder reaction to form a polycyclic compound was demonstrated.

1,2,4,5-Tetramethylenecyclohexane (**A**)[1] and its bridged derivatives **B**[2] (Fig. 1) have attracted interest in the field of structural chemistry due to their unique carbon framework and also in organic synthesis as useful intermediates. Although a variety of bridged compounds **B** were prepared and utilized in the construction of ring systems as described above, other homologues of **A**, namely, *non-bridged* tetraalkylidenecyclohexanes **C**, have not been synthesized in a practical way[3] and, accordingly, their application in organic chemistry has not been pursued. Recent progress in the intermolecular coupling of unsaturated compounds with group IV metal complexes[3,4,5,6] prompted us to revisit the synthesis of these compounds **C** by a newly introduced titanium reagent. We will illustrate herein an efficient and one-pot synthesis of tetraalkylidenecyclohexanes **4**, **5**, **6**, and **9** shown below through homo-dimerization of skip-type diynes **2** and **7** with a titanium(II) alkoxide reagent, $Ti(O^iPr)_4/2^iPrMgCl$ (**1**),[6] together with their synthetic reaction.

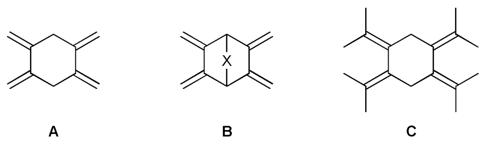
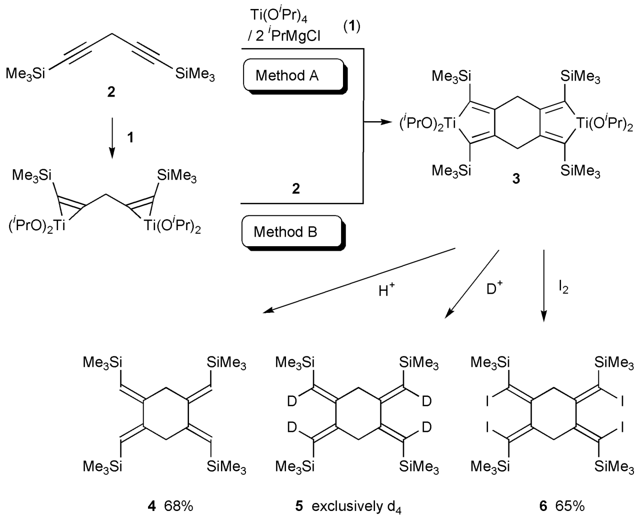


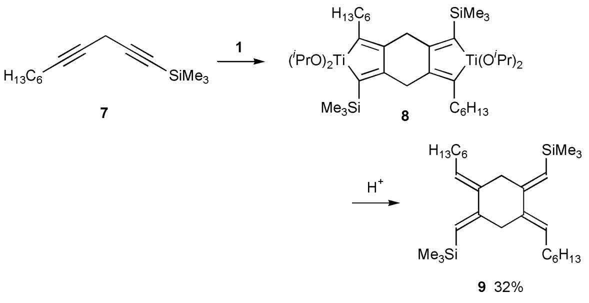
Fig. 1 1,2,4,5-Tetramethylenecyclohexane and its derivatives.

Tetraalkylidenecyclohexane **4** and its derivatives **5** and **6** were prepared from **2** by two different methods A and B,† which are formulated in Scheme 1. (i) Method A: to a mixture of diyne **2** (1 eq.) and $Ti(O^iPr)_4$ (2 eq.) in ether was added ^iPrMgCl (4 eq.) at −78 °C. The reaction mixture was allowed to slowly warm up to room temperature and was stirred overnight to complete the formation of **3**. (ii) Method B: to a mixture of **2** (0.5 eq.) and $Ti(O^iPr)_4$ (1.5 eq.) in ether was added ^iPrMgCl (3 eq.) at −78 °C and the reaction mixture was stirred at −50 °C for 4 h. Then, another half-equivalent of diyne **2** was added, and the reaction mixture was allowed to warm up to room temperature and stirred for an additional 7 h to ensure the formation of **3**. After hydrolysis of this titanacycle, the desired homo-coupling product **4** of the defined stereochemistry (M^+(*m*/*e*) 420 by GC/MS, olefin geometry established by ^1H NMR NOE study) was obtained in the same 68% yield by each of the two methods. In place of the hydrolysis, deuteriolysis gave **5** and iodinolysis afforded tetraiodide **6** as a single product.

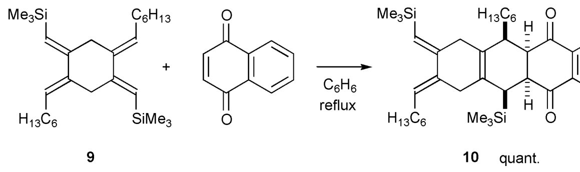
When the same reaction was applied to unsymmetrical diyne **7** [eqn. (1)], strictly one kind of homo-dimer **9** (M^+(*m*/*e*) 444, structure verified by NOE study) was isolated in 32% yield. To our surprise, even after careful examination by NMR spectroscopy, there was no evidence that another regioisomer was present in the crude reaction mixture. Although the yield falls in a moderate range, the molecular assembly leading to the formation of a single titanacycle **8** should be an interesting observation. The Diels–Alder reaction of **9** with 3 eq. of naphthoquinone proceeded smoothly in boiling benzene to give tetracyclic compound **10**‡ in quantitative yield [eqn. (2)], showing that the reaction cleanly stopped at the mono-addition stage under these reaction conditions.



Scheme 1 Preparation of tetraalkylidenecyclohexanes.



(1)



(2)

With the successful selective coupling of diynes **2** and **7** in hand, we turned our attention to a similar dimerization of skip-type enyne **11**, aiming at the preparation of 1,4-dialkylidenecyclohexanes such as **13** [eqn. (3)].[7] Actually, upon reaction with

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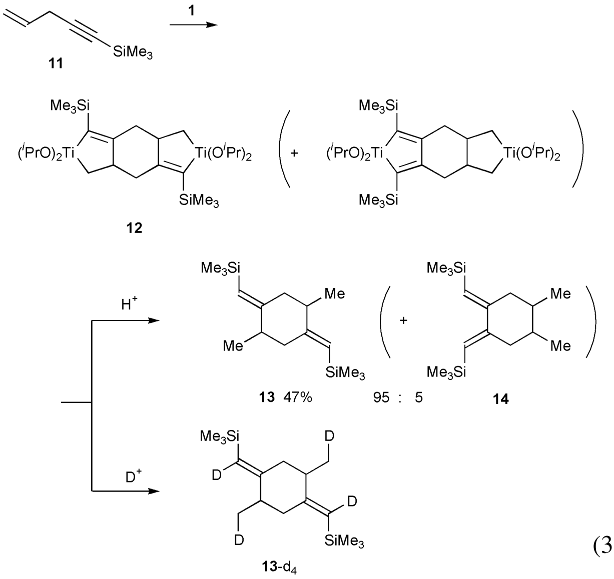
titanium reagent **1** (1.1 eq. to **11**), enyne **11** gave 1,4-dialkylidenecyclohexane **13** (M^+(*m*/*e*) 280, structure established by NOE study) in 47% yield, slightly contaminated by another isomer **14** (**13**:**14** = 95:5). However, this isomeric composition appears to vary widely depending upon experimental conditions. For example, when the amount of **1** was increased (from 1.1 eq. above) to 2 eq., the ratio **13**:**14** decreased considerably to 71:29 with a combined product yield of 85%. Thus, the reagent equivalents must be carefully observed. Deuteriolysis confirmed the presence of intermediate titanacycle **12**, which may serve for the functionalization of **13** through reaction with electrophiles. Another important feature is the fact that resultant product **13** consists of only one stereoisomer, to which we tentatively assigned a *trans* relationship (with respect to two methyl groups), under the assumption that the two titanacycle portions have the same most stable configuration.



(3)

In summary, polyalkylidenecyclohexanes were very conveniently prepared as single stereoisomers in moderate to good yields by the recently introduced titanium(II) alkoxide-mediated homo-coupling of diynes or enynes.

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Notes and references

† Typical procedure for the formation of compound **4**: method A. To a stirred solution of diyne **2** (0.24 mmol) and $Ti(O^iPr)_4$ (0.48 mmol) in 3 mL of Et_2O was added ^iPrMgCl (solution in Et_2O, 0.96 mmol) at −78 °C under argon to give a yellow homogeneous solution. The solution was slowly warmed to room temperature and stirred overnight. The reaction mixture was quenched with dilute hydrochloric acid to give the desired homo-coupling product **4**. Method B. To a stirred solution of diyne **2** (0.24 mmol) and $Ti(O^iPr)_4$ (0.72 mmol) in 4 mL of Et_2O was added ^iPrMgCl (solution in Et_2O, 1.44 mmol) at −78 °C under argon to give a yellow homogeneous solution. The solution was warmed to −50 °C and stirred at that temperature for 4 h. Then, a solution of diyne **2** (0.24 mmol in 0.5 mL of Et_2O) was added. The solution was warmed to room temperature and stirred for 7 h. The reaction mixture was quenched with dilute hydrochloric acid to give the desired homo-coupling product **4**.

‡ This product is most likely the *endo* adduct as depicted, which is amply precedented by related systems.[8]

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