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Versatile Route to *centro*-Substituted Triquinacene Derivatives: Synthesis of 10-Phenyltriquinacene

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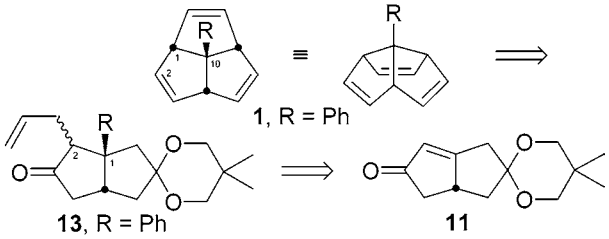
ABSTRACT



A versatile route to prepare *centro*-substituted triquinacene derivatives (1, R = various substituents), as exemplified by the preparation of 10-phenyltriquinacene (1, R = Ph), is reported. The quaternary, *centro* substituent (C-10) was installed by a trimethylsilyl chloride-promoted conjugate addition reaction of an organocuprate, derived from phenylmagnesium bromide, and the protected bicyclic enone (11). The resultant trimethylsilyl enol ether was then converted regioselectively to the C-2-allylated conjugate addition products (13, R = Ph). The allyl moiety, following oxidative cleavage of the carbon–carbon double bond, was used to elaborate the tricyclic ring system by an intramolecular aldol/acetal deprotection reaction. The product of this reaction was then converted to the target compound using a standard series of functional group transformation reactions.

Triquinacene (**1**, R = H, $C_{10}H_{10}$−tricyclo[5.2.1.0^{4,10}]deca-2,5,8-triene), a highly condensed tricyclic hydrocarbon, was first synthesized by Woodward and co-workers in 1964 (Figure 1).[1] The synthesis and study of the physical and

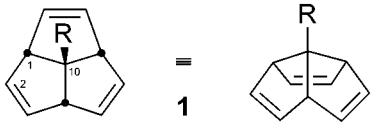


Figure 1. Triquinacene (**1**, R = H) and *centro*-(C-10)-substituted triquinacenes (**1**, R = Ph, OH, Br, CO_2H).

chemical properties of this novel hydrocarbon, and related derivatives, have been the subject of continued scientific investigation ever since.[2] Particular interest has been directed toward the photochemical [6π + 6π] dimerization of triquinacene (**1**, R = H), which was first proposed by Woodward nearly forty years ago, as a means to prepare dodecahedrane ($C_{20}H_{20}$). This transformation has not been achieved under photochemical or thermal reaction conditions or by transition metal catalysis.[2,3] The most notable efforts to resolve this long-standing objective have involved the incorporation of covalent tethers between the two triquinacene moieties.[4] In addition, the preparation of transition metal complexes to correctly position the triquinacene moieties for the dimerization reaction has been considered.[5]

In this Letter, we describe an efficient and versatile synthesis of 10-phenyltriquinacene (**1**, R = Ph) that will

(1) Woodward, R. B.; Fukunaga, T.; Kelly, R. C. *J. Am. Chem. Soc.* **1964**, *86*, 3612.
(2) Hopf, H. *Classics in Hydrocarbon Chemistry*; Wiley-VCH: Weinheim, 2000.
(3) For a review on the chemistry of dodecahedrane and related molecules, see: Paquette, L. A. *Chem. Rev.* **1989**, *89*, 1051.
(4) (a) Deslongchamps, P.; Soucy, P. *Tetrahedron* **1981**, *37*, 4385. (b) Roberts, W. P.; Shoham, G. *Tetrahedron Lett.* **1981**, *22*, 4895.

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allow for a series of related *centro*-substituted triquinacene derivatives to be prepared and studied (Figure 1). For example, the hitherto unknown 10-hydroxy- and 10-bromotriquinacene (**1**, R = OH, Br) should serve as precursors for the generation and study of the corresponding nonplanar trishomoallylic carbocation, anion, and radical.

The synthesis of triquinacene-10-carboxylic acid (**1**, R = CO_2H) is of particular interest to us in connection with a novel solution to the triquinacene dimerization problem (Figure 2). It is hoped that the photochemical dimerization

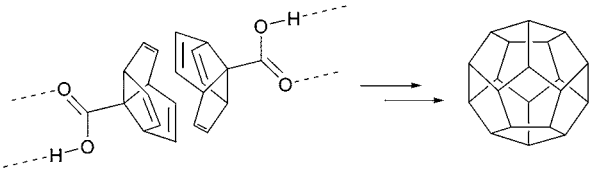

Figure 2. Proposed dimerization of triquinacene-10-carboxylic acid (**1**, R = CO_2H).

reaction could be carried out in the solid state following crystallization or cocrystallization of this compound. Here, the correct orientation of the triquinacene moieties could be achieved through directional noncovalent bonding interactions between the C-10 carboxylic acid substituents.[6,7] A subsequent double-decarboxylation reaction would then afford dodecahedrane.

A number of *centro*-substituted triquinacene derivatives have been prepared (Figure 3). Although numerous synthetic

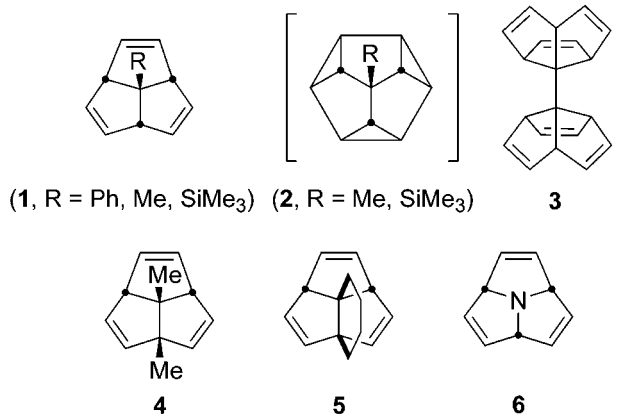

Figure 3. Known and related *centro*-substituted triquinacenes.

routes to prepare triquinacene (**1**, R = H) have been reported, no practical or versatile preparations of *centro*-substituted derivatives have been developed.[1,8] For example, 10-phenyltriquinacene (**1**, R = Ph) was elaborated from an unexpected reaction product that was isolated from a palladium-catalyzed substitution reaction of a triquinanedione system.[9] However, the yield of this novel process was relatively low. de Meijere has shown that 10-methyltriquinacene (**1**, R = CH_3) and 10-(trimethylsilyl)triquinacene (**1**, R = $SiMe_3$) can be prepared efficiently by thermal rearrangement of the corresponding diadamane derivatives **2**, but again these compounds are only available in low overall yield.[6,10] 10-Triquinacyl-triquinacene **3** has been isolated as a byproduct and in low yield from the radical dechlorination of perchlorotriquinacene.[11] The related disubstituted derivatives, 1,10-dimethyltriquinacene **4** and 1,10-cyclohexanotriquinacene **5**, have been prepared by modification of Cook's original synthetic route to triquinacene (**1**, R = H) from symmetrical precursors.[8g] More recently, a series of studies concerning the synthesis and properties of 10-azatriquinacene **6** have been reported.[7]

Our synthetic approach to *centro*-substituted triquinacene derivatives began with the Weiss−Cook condensation reaction of glyoxal **7** and dimethyl β-ketoglutarate **8** (Scheme 1). We have modified this procedure from that reported in that the bis-sodium salt, which is precipitated in the Weiss−Cook reaction, was directly subjected to the hydrolysis/decarboxylation reaction in acetic acid/aqueous hydrochloric acid in order to negate a neutralization and solvent extraction step.[12] This afforded the known bicyclic dione **9**. Reaction of dione **9** with 1 equiv of neopentyl glycol and a catalytic amount of *para*-toluenesulfonic acid provided an essentially statistical mixture of the desired monoacetal **10** (52%), the corresponding bis-acetal (21%), and the dione starting material **9** (22%). The latter two compounds could be re-equilibrated under similar reaction conditions to provide further quantities of the monoacetal **10**.[13]

The enone **11**, which could serve as a key intermediate for the synthesis of a variety of *centro*-substituted triquinacene derivatives, was then prepared in high yield on oxidation of the corresponding trimethylsilyl enol ether of the monoacetal **10** with palladium(II) acetate.[14] Unfortunately, the yield of

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(6) A related photochemical dimerization of diadamane-1-carboxylic acid, as a means to prepare dodecahedrane-1,16-dicarboxylic acid in the solid state, has been proposed; see: Bengtson, B. Ph.D. Dissertation, Universität Hamburg, Hamburg, 1986.

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(8) (a) Jacobson, I. T. *Acta Chem. Scand.* **1967**, *21*, 2235. (b) de Meijere, A.; Kaufmann, D.; Schallner, O. *Angew Chem. Int. Ed.* **1971**, *10*, 417. (c) Mercier, C.; Soucy, P.; Rosen, W.; Deslongchamps, P. *Synth. Commun.* **1973**, *3*, 161. (d) de Meijere, A. *Tetrahedron Lett.* **1974**, 1845. (e) Wyvratt, M. J.; Paquette, L. A. *Tetrahedron Lett.* **1974**, 2433. (f) Carceller, E.; Garcia, M. L.; Moyano, A.; Serratosa, F. *J. Chem. Soc., Chem. Commun.* **1984**, 825. (g) Gupta, A. K.; Lannoye, G. S.; Kubiak, G.; Schkeryantz, J.; Wehrli, S.; Cook, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 2169.

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(10) de Meijere, A. In *Cage Hydrocarbons*; Olah, G., Ed.; Wiley: New York, 1990; Chapter 4.

(11) Jacobson, I. T. *Chem. Scripta* **1974**, *5*, 227.

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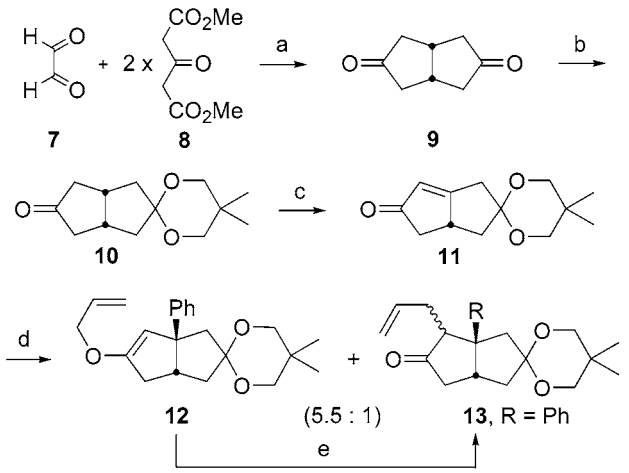
(13) Piers, E.; Karunaratne, V. *Can. J. Chem.* **1989**, *67*, 160.

(14) Dragojlovic, V. *Molecules* **2000**, *5*, 674.

Scheme 1. Synthesis of the C-2-Allylated Conjugate Addition Products (**13**, R = Ph)[a]



[a] Reagents and conditions: (a) (i) NaOH, MeOH, H_2O, rt, 16 h; (ii) HCl (aq), AcOH, reflux, 3 h, 59%. (b) neopentyl glycol, *p*-TsOH (cat.), PhH, reflux, Dean−Stark apparatus, 4 h, 52%. (c) (i) LDA, THF, −78 °C, 30 min, then TMSCl, THF, −78 °C to room temperature, 2 h; (ii) $Pd(OAc)_2$, MeCN, 0 °C to room temperature, 14 h, 91%. (d) (i) PhMgBr, CuI, TMSCl, THF, 0 °C, 3 h, then Et_3N (excess, quench); (ii) MeLi, THF, 0 °C, 30 min, then allyl bromide, HMPA, 0 °C to room temperature, 16 h, 65% (**12** + **13**, R = Ph, 5.5:1). (e) PhMe, reflux, 3 days, 96%.

this process on employment of a substoichiometric amount of palladium(II) acetate with benzoquinone or dichlorodicyanoquinone as a co-oxidant proved to be less than satisfactory.[15] However, we have developed an alternative dehydrogenation protocol that is somewhat lower yielding but does not involve the stoichiometric use of palladium(II) acetate. It was found that the monoacetal **10** could be converted to the corresponding α-phenylselenide that in turn could be oxidized with hydrogen peroxide to afford enone **11** in 57% overall yield.[16,17]

The trimethylsilyl chloride-promoted conjugate addition reaction of enone **11** and an organocuprate, prepared from phenylmagnesium bromide and copper(I) iodide, smoothly afforded the conjugate addition product as the corresponding trimethylsilyl enol ether.[18] This intermediate was then treated with methyllithium to generate the corresponding lithium enolate, which was reacted with allyl bromide in the presence of hexamethylphosphoramide. This two-step procedure afforded a chromatographically separable ∼5.5:1 mixture of the O- and C-2-allylated adducts (**12** and **13**, respectively, R = Ph) in 65% combined yield. A nonallylated conjugate addition product was also isolated in 15% yield, and no diallylation reaction products were observed. The minor C-2-allylated adducts (**13**, R = Ph) were formed as a ∼1:1 mixture of diastereomers.[19] Conjugate addition reactions of enone **11** and a variety of organocuprates can also be achieved in the absence of trimethylsilyl chloride. However, the resultant intermediate copper enolates in these reactions have proved to be unreactive toward a number of alkylating agents.[20] The major O-allylated adduct **12** could be cleanly converted to the desired C-*2*-allylated adducts (**13**, R = Ph), by means of a Claisen rearrangement, on heating at reflux in toluene (96% yield). In this case, the reaction product was isolated as a ∼3:2 mixture of diastereomers. These two combined processes have allowed for the regioselective installation of the allyl moiety at C-2 of this bicyclic system for subsequent elaboration of the third ring of the target compound. Interestingly, no significant stereochemical preference was observed for the delivery of the allyl moiety to the convex or concave face of this *cis*-bicyclo[3.3.0]octane ring system. This can be attributed to the additional steric hindrance provided by the phenyl substituent that is positioned over the convex face of this highly congested ring system.

The formation of the tricyclic ring system of the target compound was achieved by first carrying out a dihydroxylation/oxidative cleavage reaction of alkenes (**13**, R = Ph) that afforded the corresponding aldehydes **14** (Scheme 2).[8g,21] The synthesis of the parent triquinacene ring system by Deslongchamps and co-workers involved a tandem acetal deprotection/intramolecular aldol reaction that was performed in THF solution with dilute hydrochloric acid.[8c] Unfortunately, these reaction conditions failed to effect either the deprotection or the cyclization reaction of compound **14**.

A series of studies were then undertaken to identify suitable reaction conditions for the tandem acetal deprotection/intramolecular aldol reaction. Treatment of compound **14** with a catalytic amount of *para*-toluenesulfonic acid in aqueous acetone cleanly effected the desired acetal deprotection reaction but did not effect the desired aldol reaction. Substitution of reagent-grade acetone for aqueous acetone in the above reaction led to slow cyclization of compound **14** without deprotection of acetal moiety and cleanly afforded the tricyclic acetal **15**. Subsequent addition of water to the reaction mixture finally effected the deprotection of the acetal and afforded the required tricyclic diketo alcohol **16** as a ∼7:3 mixture of diastereomers in good yield (79%). The tricyclic acetal **15** was also isolated from this reaction in 14% yield as a ∼5:1 mixture of diastereomers. This acetal could be recycled and converted to the required aldol product **16** in 92% yield. The excellent overall yield of this process indicates that the two diastereomers of the starting material are efficiently interconverted under the reaction conditions.

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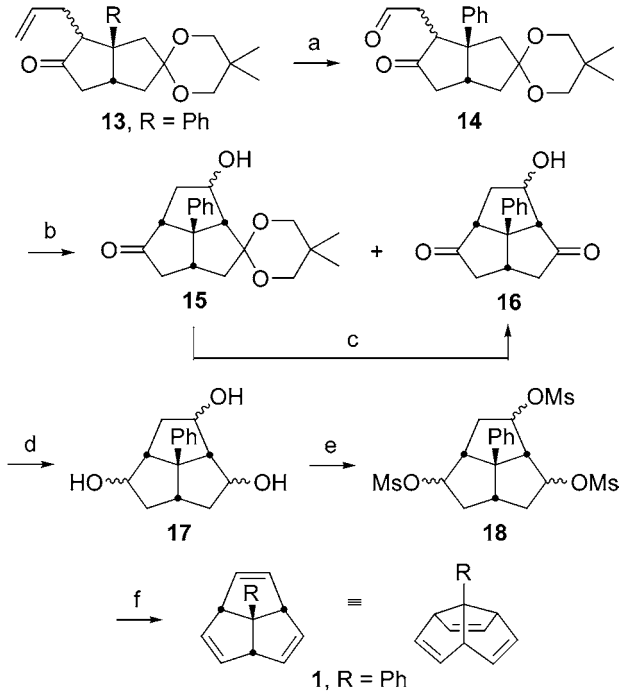
(16) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Org. Chem.* **1974**, *39*, 2133.
(17) Dehydrogenation of the monoacetal **10** or oxidation of the corresponding trimethylsilyl enol ether with *ortho*-iodoxybenzoic acid (IBX) under a variety of experimental conditions afforded only trace quantities of the required product; see: (a) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 993. (b) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 996.
(18) Bertz, S. H.; Miao, G.; Rossiter, B. E.; Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11023 and references therein.
(19) For an example of a conjugate addition reaction of a related bicyclic enone that was not reacted with an alkylating agent, see: Paquette, L. A.; Lau, C. J. *Synth. Commun.* **1984**, *14*, 1081.
(20) (a) Coates, R. M.; Sowerby, R. L. *J. Am. Chem. Soc.* **1971**, *93*, 1027. (b) Coates, R. M.; Sandefur, L. O. *J. Org. Chem.* **1974**, *39*, 275.
(21) Pappo, R.; Allen, D. S. Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

Scheme 2. Synthesis of 10-Phenyltriquinacene (1, R = Ph)[a]



[a] Reagents and conditions: (a) OsO_4 (cat.), $NaIO_4$, *p*-dioxane, H_2O, rt, 6 h, 85%; (b) *p*-TsOH (cat.), acetone, rt, 5 days, then H_2O, 2 days, 14% (**15**) and 79% (**16**); (c) *p*-TsOH (cat.), acetone/H_2O (2/1), rt, 2 days, 92%; (d) BH_3·THF, THF, 0 °C to room temperature, 16 h, 77%; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C to room temperature, 2 h; (f) activated neutral Al_2O_3, CH_2Cl_2, rt, 3 days, 44% (over two steps).

The synthesis of 10-phenyltriquinacene (**1**, R = Ph) was completed by modification of the protocol developed by Cook and co-workers for the preparation of the parent hydrocarbon, triquinacene (**1**, R = H).[8g] Reduction of the diketo alcohols **16** with borane−tetrahydrofuran complex afforded the triols **17** as a complex mixture of stereoisomers in 77% yield. Activation of this mixture of triols by conversion to the corresponding trimesylates **18** was then readily achieved under standard reaction conditions. Finally, elimination of the three mesylate moieties was accomplished on stirring the crude mesylates **18** with a slurry of highly activated neutral alumina in dichloromethane.[22] This afforded 10-phenyltriquinacene (**1**, R = Ph) in 44% yield from the triols **17**. The spectral data and physical properties of this material were identical to those reported previously.[9]

In conclusion, a practical and potentially versatile synthetic route to *centro*-substituted triquinacene derivatives has been developed as exemplified by the preparation of 10-phenyltriquinacene (**1**, R = Ph). This synthesis was achieved in 12 steps from glyoxal **7** and dimethyl β-ketoglutarate **8** in ~5% overall yield. The quaternary, *centro* substituent (C-10) was installed in this highly condensed ring system by means of a conjugate addition reaction. The extension of this synthetic route to prepare other *centro*-substituted triquinacene derivatives, particularly those capable of engaging in noncovalent bonding interactions, is underway and will be reported in due course. Current studies involve the conjugate addition reactions of protected hydroxymethyl anion equivalents (MCH_2OP) to enone **11** in order to prepare triquinacene-10-carboxylic acid (**1**, R = CO_2H).[23] Subsequent elaboration of the latter compound will allow for the preparation of the remaining target *centro*-substituted triquinacene derivatives, 10-hydroxy- and 10-bromotriquinacene (**1**, R = OH, Br), for the study of their physical and chemical properties.

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Supporting Information Available: Detailed experimental procedures and product characterization data for all of the compounds synthesized, as well as ^1H and ^{13}C NMR spectra for compounds **12**, **13** (R = Ph), **14**−**16**, and **1** (R = Ph). This material is available free of charge via the Internet at http://pubs.acs.org.

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