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Concise synthesis of triasteranones from barbaralones

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Triasteranes are underexplored, topologically appealing polycyclic compounds with a star-like shape that have been challenging to synthesize. Herein, we report the concise syntheses of triasteranone derivatives from readily accessible barbaralones.

Bridged or caged polycyclic hydrocarbons are of significant interest because of their unique, often topologically appealing structures.[1] Their rigid, often highly strained frameworks are useful for studying bonding and reactivity. Their challenging synthesis continues to inspire advances in synthetic methodology, and they have applications in medicinal chemistry,[1b,c] supramolecular chemistry and materials science,[1c] and as energetic materials.[2]

Asteranes are interesting polycyclic hydrocarbons consisting of two carbon–carbon bonds (in the case of diasterane) or two cycloalkanes linked by a carbon atom at every position (Fig. 1A).[3–6] This arrangement results in a star-like shape with every lateral face being a cyclohexane in a boat conformation. First described by Musso and co-workers in 1965,[4a] asteranes have been studied by the Musso group and others.[3–6] Recently, there has been interest in triasteranes as intermediates in the synthesis of stable, neutral, homoaromatic hydrocarbons such as **1** and **2**,[4o,p] and as a member of a network of 13 distinct polycycles accessed by "shapeshifting" skeletal evolution from a common starting material (Fig. 1B).[4q] DFT calculations have also suggested that perfluorinated triasterane **3** (which has not yet been prepared) exhibits a strong perfluoro cage effect due the low-energy,[7] overlapping, inward-pointing lobes of its C–F σ* orbitals, and should therefore be able to encapsulate an electron.[7,8]

Despite their intriguing structures, triasteranes are challenging to synthesize.[4] For example, the synthesis of triasteranone (**4**) requires seven steps from cyclohexa-1,4-diene and diethyl diazomalonate, which was then converted into triasterane by a Wolff–Kishner reduction (Fig. 1C, top).[4a] Grohmann and co-workers reported the three-step synthesis of the triasterane

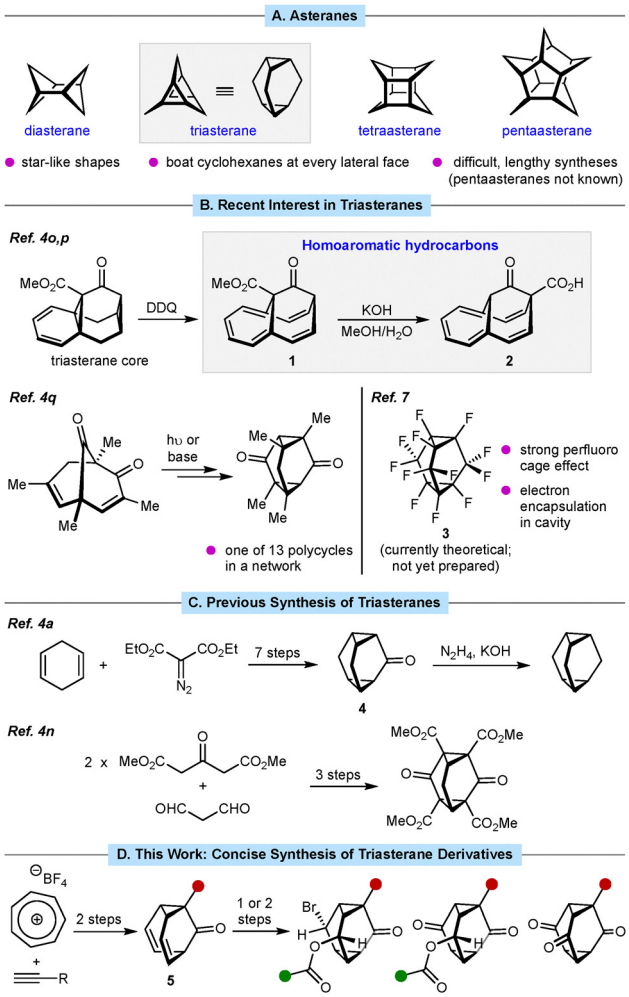

Fig. 1 Asteranes; structures, recent interest, and this work.

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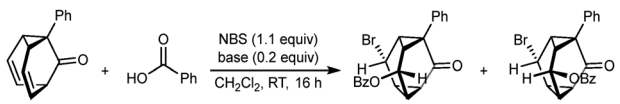
skeleton from commercial compounds, but only one example was described and the product is too densely functionalized for wide synthetic applicability (Fig. 1C, bottom).[4n] The difficulty in preparing triasteranes has hindered the study of their properties, reactivities, and applications, and more efficient methods are therefore required. Herein, we report a concise synthesis of substituted triasteranone derivatives in just three or four steps from commercial compounds (Fig. 1D).

Our approach exploits barbaralones **5**, which are fluxional molecules that undergo Cope rearrangement between constitutional isomers,[9] as versatile triasteranone precursors (Fig. 1D). Although Vedejs demonstrated the viability of this concept through the dibromination of barbaralone to give diastereomeric triasteranone dibromides in 72% combined yield, only one example was reported and there were no follow-up studies.[4d,f] This limitation likely stemmed from the then-challenging synthesis of barbaralones. However, in 2016, the Echavarren group reported a practical two-step synthesis of barbaralones from commercially available tropylium tetrafluoroborate and terminal alkynes (Fig. 1D).[10a] We recognized that integrating these methods could provide a streamlined, general access to triasteranones, thus opening the door to greater investigation of these underexplored compounds.

We first targeted triasteranones containing two different functional groups by the bromoesterification[11] of barbaralones (Table 1). No reaction occurred when barbaralone **5a**[10a] was stirred with NBS (1.1 equiv.) and benzoic acid (2.0 equiv.) in CH_2Cl_2 at room temperature for 16 h (entry 1). However, repeating the reaction with the addition of DABCO (20 mol%) gave a 6.3 : 1 inseparable mixture of diastereomeric triasteranones **6a** and **6a′** in 92% NMR yield (entry 2).[12] The relative configuration of the major isomer **6a** was assigned by comparison of its NMR data with that of **6b**, the stereochemistry of which was determined by X-ray crystallography (Scheme 1).[12] For a structural analysis of **6b** that covers substituent exit vector angles and distances between substituents, see the SI. The stereochemistry of **6a′** was assigned from NOESY NMR data (see the SI). Other bases such as quinuclidine, DBU, and pyridine gave inferior results (entries 3–5).

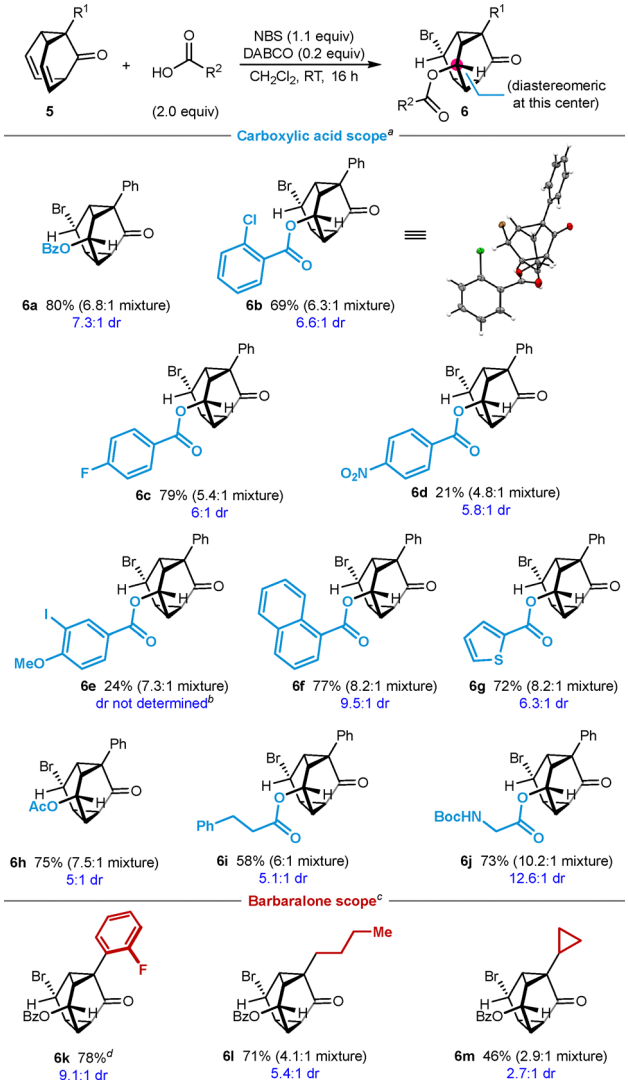
Table 1 Evaluation of bases in the bromoesterification of barbaralone **5a**[a]



5a (2.0 equiv) 6a 6a′

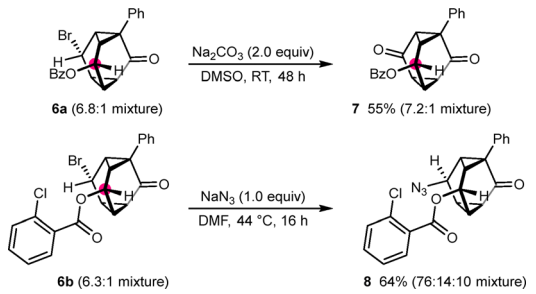
Entry	Base	Yield[b] (%)	dr (**6a**:**6a′**)[c]
1	None	—	
2	DABCO	92	6.3 : 1
3	Quinuclidine	69	4.1 : 1
4	DBU	66	5.2 : 1
5	Pyridine	61	5.2 : 1

[a] Conducted with **5a** (0.10 mmol) in CH_2Cl_2 (1 mL). [b] Combined yield of **6a** and **6a′** as determined by ^{1}H NMR analysis of the crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by ^{1}H NMR analysis of the crude reaction mixtures.



Scheme 1 Synthesis of triasteranones by the bromoesterification of barbaralones. The diastereomeric ratios (dr) of the reactions were determined by ^{1}H NMR analysis of the crude reactions. Yields are of isolated products, obtained as mixtures of diastereomers in the ratio indicated in parentheses. [a] Conducted with **5a** (0.30 mmol) in CH_2Cl_2 (1.5 mL). [b] The dr could not be determined from the crude mixture due to the complexity of the ^{1}H NMR spectrum. [c] Conducted with **5** (0.20 mmol) in CH_2Cl_2 (1 mL). [d] Product **6k** was isolated free from the minor diastereomer.

Barbaralone **5a** reacted with various (hetero)aromatic carboxylic acids to give triasteranones containing 2-chlorophenyl (**6b**), 4-fluorophenyl (**6c**), 4-nitrophenyl (**6d**), 3-iodo-4-methoxphenyl (**6e**), 1-naphthyl (**6f**), or 2-thienyl groups (**6g**). The diastereoselectivities of the reactions as determined by ^{1}H NMR analysis of the crude mixtures ranged from 6 : 1 dr (**6c**) to 10 : 1 dr (**6g**). The products were isolated in up to 79% yield as inseparable mixtures of diastereomers in ratios between 4.8 : 1 (**6d**) and 8.2 : 1 (**6f**). The yields were lower in the reactions producing **6d** (21% yield) and **6e** (24% yield) as significant starting materials remained. Aliphatic carboxylic acids such as acetic acid, 3-phenylpropionic acid, and *N*-Boc glycine also reacted with **5a** to give triasteranones **6h–6j**, respectively, with the latter giving the highest diastereoselectivity

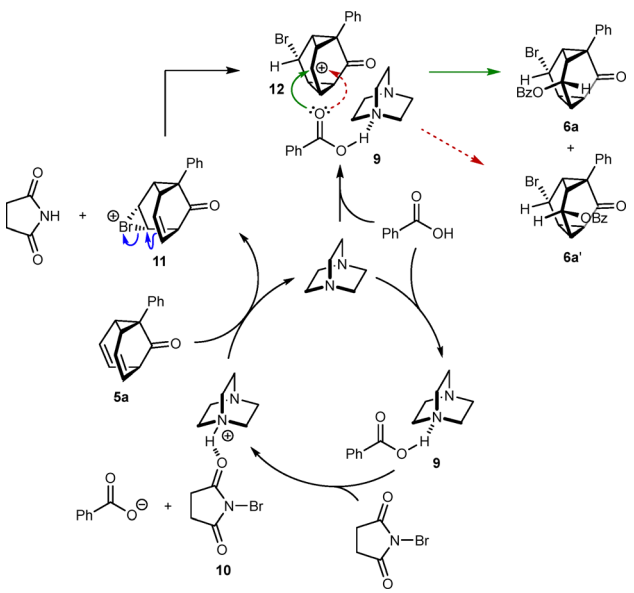


Scheme 2 Further manipulations.

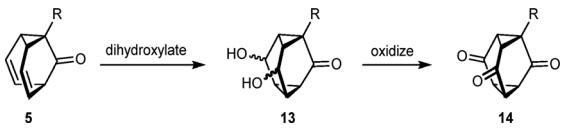
observed (12.6 : 1 dr). Barbaralones containing 2-fluorophenyl, *n*-butyl, or cyclopropyl groups successfully reacted with benzoic acid to give triasteranones **6k–6m**, respectively, in 46–78% yield. Comparison of the reactions producing **6a** and **6k–6m** shows that sterically more hindering barbaralone substituents result in higher diastereoselectivities.

Further functionalization of the products was then investigated (Scheme 2). Reaction of triasteranone **6a** (a 6.8 : 1 diastereomeric mixture) with DMSO and Na_2CO_3 (2.0 equiv.) at room temperature resulted in Kornblum oxidation to give triasteranedione **7** in 55% yield. Treatment of **6b** (6.3 : 1 mixture of diastereomers) with NaN_3 (1.0 equiv.) in DMF at 44 °C for 16 h gave azide **8** in 64% yield as a 76 : 14 : 10 mixture of diastereomers. The stereochemistry of the major diastereomer of **8** is consistent with nucleophilic substitution of the major diastereomer of **6b** by an S_N2 pathway. However, the formation of two other diastereomers suggests that other mechanisms of nucleophilic substitution could also be operative (see the SI).

A tentative mechanism for the bromoesterifications, using barbaralone **5a** and benzoic acid as reactants, is shown in Scheme 3. First, hydrogen bonding of DABCO to benzoic acid gives **9**, which reacts with NBS to give benzoate anion and the more electrophilic brominating agent **10**, in which NBS is



Scheme 3 Tentative mechanism of bromoesterification of barbaralones.

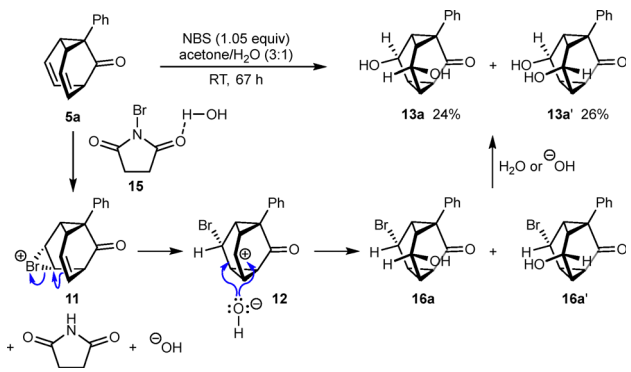


Scheme 4 Strategy to prepare triasteranetriones from barbaralones.

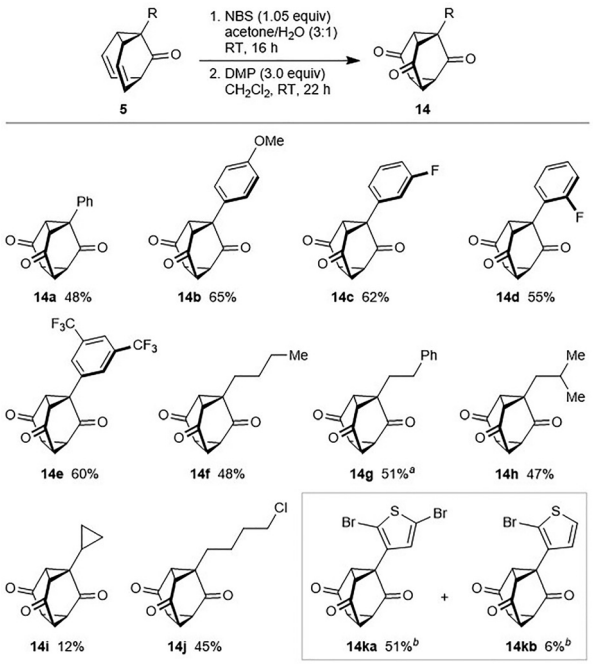
hydrogen-bonded to DABCO ammonium ion. This activation is essential, as evidenced by the lack of reaction of **5a** with NBS and benzoic acid without DABCO (Table 1, entry 1), which is also consistent with the greater acidity of DABCO ammonium ion ($pK_a \sim 8.9$ in DMSO[13]) compared with benzoic acid ($pK_a \sim 11.0$ in DMSO[14]). Bromination of **5a** with **10** liberates succinimide and gives cyclic bromonium ion **11**, which is ring-opened by the remaining alkene to form triasteranyl carbocation **12**. The diastereoselectivity depends on the base used (Table 1), which suggests the base is directly involved in the C–O bond-forming step. We propose that nucleophilic attack of carbocation **12** occurs from the carbonyl group of complex **9** to give diastereomeric triasteranones **6a** and **6a′**. However, we do not rule out other mechanisms.[15]

We next investigated whether barbaralones **5** could be dihydroxylated to give triasteranone diols **13**, which could then be oxidized to give substituted triasteranetriones **14** (Scheme 4). The parent, unsubstituted triasteranetrione (**14** with R = H) was first prepared by McDonald and Dreiding in the 1970s using lengthy routes,[4g,h] and it has been used to study the effect of π-accepting substituents on the average C–C bond length within cyclopropanes.[4l,16] However, to our knowledge, substituted triasteranetriones have not been prepared previously.

Our approach for the dihydroxylation of barbaralones employs NBS and water in the hope that the initial bromohydroxylation products **16** could react further with water to give diols **13** (Scheme 5). Indeed, reaction of barbaralone **5a** with NBS (1.05 equiv.) in acetone/H_2O (3 : 1) at room temperature for 67 h gave diastereomeric diols **13a** (24% yield) and **13a′** (26% yield).[12] In contrast to the bromoesterifications (Scheme 1), no base is required. Also, no reaction occurs when **5a** is treated with NBS in acetone in the absence of water. A possible mechanism for this process follows a similar pathway to that shown in Scheme 3 to give triasteranyl carbocation **12**, but here the brominating agent is likely to be **15**, where NBS is activated



Scheme 5 Tentative mechanism of dihydroxylation of barbaralones.



Scheme 6 Synthesis of triasteranetriones. Yields are of isolated products, quoted over two steps. DMP = Dess–Martin periodinane. [a] Using NBS (1.24 equiv.) and DMP (3.55 equiv.). [b] Using NBS (3.0 equiv.).

by hydrogen bonding to water. Attack of **12** by hydroxide anion gives diastereomeric bromoalcohols **16a** and **16a′**. Finally, nucleophilic substitution of the bromides with water or hydroxide anion, most likely by an S_N2 mechanism, gives diols **13a** and **13a′**.

Subsequently, we found the reaction time could be reduced to 16 h, and oxidation of the resulting crude mixture of diols **13a** and **13a′** with Dess–Martin periodinane (DMP, 3.0 equiv.) then gave triasteranetrione **14a** in 48% yield over two steps (Scheme 6).[12] The scope of this process was investigated using different barbaralones,[10] which gave triasteranetriones in up to 65% yield over two steps. As well as **14a**, the process can be used to prepare triasteranetriones with other aromatic substituents such as 4-methoxyphenyl (**14b**), 3-fluorophenyl (**14c**), 2-fluorophenyl (**14d**), and 3,5-bis(trifluoromethyl)phenyl groups (**14e**). Triasteranetriones with *n*-butyl (**14f**), 2-phenylethyl (**14g**), isobutyl (**14h**), cyclopropyl (**14i**), or 4-chlorobutyl groups (**14j**) can also be prepared, although the yield of **14i** was only 12% because it was accompanied by a complex mixture of unidentified products and it was difficult to extract from the aqueous layer during workup. A 3-thienyl group in the barbaralone was found to undergo competitive bromination, but the use of 3.0 equivalents of NBS in the first step gave dibrominated thiophene-containing triasteranetrione **14ka**[12] in 51% yield and monobrominated product **14kb** in 6% yield.

In summary, we have described the synthesis of substituted triasteranones, triasteranediones, and triasteranetriones from readily accessible barbaralones. At just three or four steps, this route provides access to triasteranones in a much more concise fashion compared with previous methods,[4] which enables more extensive investigation of these fascinating compounds.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article has been included as part of the supplementary information (SI) and the Nottingham Research Data Management Repository at: http://doi.org/10.17639/12985. Supplementary information: experimental procedures, characterization data for new compounds, and copies of NMR spectra. See DOI: https://doi.org/10.1039/d6cc00474a.

CCDC 2522306 (**6b**), 2522307 (**13a′**), 2522308 (**14a**), 2522309 (**14g**) and 2522310 (**14ka**) contain the supplementary crystallographic data for this paper.[17a–e]

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