Seven-Membered Rings through Metal-Free Rearrangement Mediated by Hypervalent Iodine

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Abstract: A versatile and metal-free approach for the synthesis of carbocycles and of heterocycles bearing seven- and eight-membered rings is described. The strategy is based on ring expansion of 1-vinylcycloalkanols (or the corresponding silyl or methyl ether) mediated by the hypervalent iodine reagent HTIB (PhI(OH)OTs). Reaction conditions can be easily adjusted to give ring expansion products bearing different functional groups. A route to medium-ring lactones was also developed.

Keywords: hypervalent iodine; ring expansion; rearrangement; seven-membered ring; antiproliferative activity

1. Introduction

The presence of seven-membered rings in compounds with remarkable biological activity continuously challenges organic chemists to develop efficient method for their preparation [1–14] (for examples of
natural or designed compounds, see Figure 1). Construction of seven-membered rings is relatively more difficult than the corresponding process for five- and six-membered rings, mainly because cyclization reactions have the inherent drawback of entropic factors and transannular interactions [1,3,15]. Nevertheless, a variety of different methodologies were envisioned to circumvent these problems, such as palladium-catalyzed intramolecular reactions, and radical and electrophilic cyclizations [1–4,7,9–12]. Besides the palladium-catalyzed processes, other metal-mediated reactions were investigated and ring-closing metathesis and cycloadditions are probably the most used in the synthesis of seven- and eight-membered rings [5–10,12,16]. Another approach is a ring expansion reaction [12,17–19], which has the main advantage to avoid entropic factors and high-diluted conditions [1,15]. One possible strategy to promote a ring expansion is an oxidative rearrangement that can be performed with transition metals, such as palladium(II) [17], mercury(II) [20], and thallium(III) [21,22]. An alternative to prevent the use of these metals is a hypervalent iodine reagent that promotes several different reactions in an efficient manner, such as formation of C–C bonds, stereoselective oxidations, and many important functional group transformations, including asymmetric reactions [23–30]. Although oxidative rearrangements mediated by hypervalent iodine have been reported in many publications, systematic studies regarding ring expansion reactions are scarce [27]. The ring expansion of methylene derivatives mediated by PhI(OH)OTs (HTIB or Koser’s Reagent) has been investigated by Justik and Koser for the synthesis of six-, seven-, and eight-membered ring carbocyclic compounds [31,32]. This protocol was subsequently applied in the total synthesis of both isomers of ar-himachalene (Figure 1) [33]. This article presents a versatile and metal-free approach for the synthesis of molecules bearing a seven-membered ring, through a ring expansion reaction [34].

Figure 1. Compounds bearing seven-membered ring fused to aromatic ring.

2. Results and Discussion

The substrates required for the ring expansion reactions were prepared in an efficient manner. The reaction of 1-tetralone (1a) with CH₂=CHMgBr gave the unsaturated 1-tetralol 2a, in 89% yield [35]. Considering the possible instability of the tertiary benzylic and allylic alcohol 2a, we decided to protect it as the trimethylsilyl (TMS) ether. The protocol using trimethylsilyl chloride/hexamethyldisilazane (TMSCl/HMDS) in reflux of hexane was applied to 2a, giving the desired product 3a in only 11% yield. However, using HMDS in the presence of a catalytic amount of I₂, as reported by Karimi and Golshani [36], was possible to obtain cleanly 3a in 99% yield (Scheme 1).
Scheme 1. Preparation of the unsaturated TMS ether 3a. HMDS: hexamethyldisilazane and TMSCl: trimethylsilylchloride.

The above two-step sequence was applied to several ketones, leading to 3b-1. We were also interested in the behavior of alkyl ethers. Thus, the methyl ether 4a was prepared treating 2a with KOH/MeI (Figure 2) [37].

Figure 2. Structure of substrates 3b-1 and 4a.

We first performed a detailed investigation on the reactivity of the TMS-protected 1-vinylcycloalkanol 3a. Thus, treatment of 3a with HTIB in CH$_3$CN, in trimethylorthoformiate or without solvent [38] led to a complex mixture of compounds. Fortunately, when the unsaturated TMS-ether 3a was treated with HTIB in MeOH [31] in the presence of $p$-TsOH, thin layer chromatography (TLC) analysis indicated the cleavage of the labile TMS-group. Then, the alcohol 2a formed in the medium reacted with iodine(III), giving the ring expansion product 5a, in 60% yield (Table 1, Entry 1). The methoxy-ketone 5a would be originated from 3a in four steps. The first would be the acid-catalyzed deprotection of the TMS group, giving 2a, on which the electrophilic addition of iodine(III) to the double bond would give the cation 9. Migration of the aryl carbon would lead to 10. A reductive solvolysis on 10 would produce the methoxylated ketone 5a (Scheme 2). On this step occurs the highly favorable transformation of the hypervalent iodine into the normal valency compound PhI. Higher temperatures and longer reaction times promote an acid-catalyzed elimination of MeOH from 5a, furnishing the enone 6a, together with the dimer 7a (entry 2). TLC analysis showed that 7a is formed after the work-up. This result is slightly different from that using Tl(III), which gives only the enone 6a from 3a [22].
Table 1. HTIB-Mediated Ring Expansion of 3a. HTIB: [Hydroxy(tosyloxy)iodo]benzene; \textit{p}-TsOH: \textit{p}-Toluenesulfonic acid.

| Entry | Conditions | Product (Yield) |
|-------|------------|----------------|
| 1     | 1.0 equiv HTIB, 20 mol\% \textit{p}-TsOH, MeOH, \textit{−}72 °C to rt, 2 h | ![Structure 5a](image) (60\%) |
| 2     | 1.0 equiv HTIB, MeOH, \textit{−}72 to 30 °C, 2.5 h | ![Structure 6a](image) + 7a (72\%, 4:1) |
| 3     | (1) 1.0 equiv HTIB, MeOH, \textit{−}72 to 30 °C, 2.5 h; (2) 2 weeks | ![Structure 7a](image) (55\%) |
| 4     | 2.5 equiv HTIB, MeOH, rt, 2 h | ![Structure 8a](image) (75\%) |

On standing, the mixture 6a/7a gave pure crystals of 7a, in 55\% yield from 3a (Table 1, entry 3), whose structure was assigned by X-ray analysis [34]. The pentacyclic compound 7a is formed from the 1-vinylcycloalkanol derivative 3a in a single operation through a tandem ring-expansion/hetero-Diels-Alder reaction [39,40]. We envisioned that 7a could be used to obtain a medium ring lactone [41,42]. Indeed, the oxidative cleavage of the double bond of 7a could be performed with RuCl3/NaIO4, giving the eleven-membered ring keto-lactone 11a (Scheme 3). In summary, the commercially available 1-tetralone (1a) was transformed in only four steps into 11a, which bears a spiro seven-membered ring and a medium-ring lactone. Thus, in this short sequence of steps, the molecular complexity is greatly increased, because several reactions took place in a few operations.
Since the double bond of enone 6a is prone to further oxidation, we decided to investigate the reaction of 3a with excess of oxidant. When 3a was treated with 2.5 equiv of HTIB, a tandem ring expansion/addition of MeOH gave the dimethoxy-ketone 8a (Table 1, entry 4). An iodine(III)-mediated electrophilic addition of MeOH to the enone 6a would give 8a. In summary, different ring expansion products 5a–8a can be obtained from the same substrate (3a) by modification of the reaction conditions.

After exploring the oxidation of 3a with iodine(III) under several conditions, we checked if the protection as a silyl ether was really required. The desired dimethoxy-ketone 8a was also obtained when either 2a or 4a were treated with HTIB (Scheme 4). In conclusion, the presence of the TMS group is not essential for the ring expansion, although higher yields of the desired product were observed from 3a (75%) than from 2a or from 4a (65%–67%). However, the protection of the tertiary benzylic and allylic alcohol 3a as a TMS ether greatly facilitate the storage of the substrate and we decide to do this for all substrates.

A substituent in the aromatic ring can alter the migratory aptitude of the migrating carbon, which may influence the yield of the rearrangement product. For example, a correlation between yield of the product and migratory aptitude was noted by us in Tl(III)-mediated ring contraction of 1,2-di-hydronaphthalenes [43]. Thus, we investigated the ring expansion of 3 with different groups in the aromatic ring. Alkyl groups in the aromatic ring can be problematic in reactions with hypervalent iodine [44,45]. Fortunately, the TMS-protected alcohol 3b, which bears methyl groups, gave the dimethoxy ketone 8b (Table 2, Entry 1) in a similar yield to the non-substituted substrate 3a. A methoxy group at the meta position could decrease the migratory aptitude of the migrating carbon. The value of the Hammett constant $\rho_m$ for OMe is 0.11. Hence, a lower yield of the ring expansion product could be expected. However, the reaction of 3c–d with HTIB led to the corresponding ring expansion products 8c–d, respectively, in comparable yield (Entries 2 and 3). A methoxy group in the para position of the migrating carbon increases the migratory aptitude, which could accelerate the rearrangement. In our experience, this is usually a beneficial effect [43,46]. However, the reaction with
3e gave the ring expansion product 8e, in only 10% yield (entry 4). After some experimentation, we found that treating 3e with HTIB in a mixture of AcOEt/MeOH gave 8e, in 67% yield (Entry 5).

**Table 2.** HTIB-Promoted Tandem Ring Expansion/Addition in MeOH. HTIB: [Hydroxy(tosyloxy)iodo]benzene; TMS: trimethylsilyl.

| Entry | Substrate | Products (Isolated Yield) |
|-------|-----------|---------------------------|
| 1     | ![3b](image) | ![8b](image) (72%) |
| 2     | ![3c](image) | ![8c](image) (66%) |
| 3     | ![3d](image) | ![8d](image) (51%) |
| 4     | ![3e](image) | ![8e](image) (10%) |
| 5<sup>a</sup> | ![3e](image) | ![8e](image) (67%) |
| 6<sup>a</sup> | ![3f](image) | ![5f](image) (76%, 4:1) + ![8f](image) |
| 7<sup>b</sup> | ![3g](image) | ![8g](image) (65%) |
Table 2. Cont.

| Entry | Substrate | Products (Isolated Yield) |
|-------|-----------|--------------------------|
| 8     | ![Image](image1.png) 3h | ![Image](image2.png) 8ha (44%) + ![Image](image3.png) 8hb (16%) |
| 9     | ![Image](image4.png) 3i | ![Image](image5.png) 8i (47%) + ![Image](image6.png) 13i (30%) |
| 10    | ![Image](image7.png) 3j | ![Image](image8.png) 5j (72-88%) + ![Image](image9.png) 14j |
| 11    | ![Image](image10.png) 3k | ![Image](image11.png) 15k (75%) |
| 12 b  | ![Image](image12.png) 3l | ![Image](image13.png) 8l (69%) |

*AcOEt/MeOH (2:1), −72 °C–rt; MeOH, 0–50 °C.

The same solvent mixture (AcOEt/MeOH) was also used in the reaction of 3f. In this case, a mixture of the seven-membered ring compounds 5f, 8f and 12f were isolated in very good overall yield (Entry 6). Compounds 5f and 8f could not be separated from each other by chromatography column or HPLC. The proposed mechanism for the formation of 12f was based on desaromatization reactions previously described in literature [47,48] (Scheme 5). The first step is the transformation of 3f into the seven-membered ring compound 5f, as shown in (Scheme 2), followed by the formation of the charge transfer complex 16 from 5f and HTIB. A single-electron-transfer (SET) oxidation of 16 yields the cation radical 17. Species 17 suffers a MeOH attack from the less hindered convex face and at less hindered carbon 4a (Figure 3), giving the radical 18. A second SET leads to carbocation 19, which
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reacts with the solvent yielding 20. The enone 12f is formed after an acid hydrolysis of 20 catalyzed by acid. The relative configuration of 12f was assigned by NMR analysis, including NOESY, HMBC and HSQC (see Supplementary Information for details).

Scheme 5. Mechanism for the Formation of 12f.

Figure 3. Structure of 17.

The reaction of the bromo-substituted substrate 3 g with HTIB needed heating until 50 °C to furnish the ring expanded product in good yield (Table 2, Entry 7). As expected, a withdrawing group as bromide in meta position to migrating carbon decreases its aptitude to migration and, thus, more energetic conditions were necessary. Substrate 3h was exposure to HTIB giving 8 ha/b in 44 and 16%, respectively (Entry 8). The stereoselectivity is determined in the electrophilic addition of iodine(III) to the enone 22. This step occurs preferentially through the less hindered face (Scheme 6).
The possibility of using a ring expansion reaction to prepare eight-membered rings was also investigated. Substrate 3i was treated with HTIB, giving the desired eight-membered ring compound 8i in 47% yield, together with the unsaturated ether 13i (entry 9). The relative configuration of 13i was assigned based on NMR data of related compounds [49]. This route can be useful to obtain eight-membered ring derivatives, because only three steps are necessary to obtain 8i from the commercially available benzosuberone. The first step in the formation of 20i (Scheme 7) is a ligand exchange from HTIB with 25, giving 26. A sequence of protonation of 26 and dehydration of 27 lead to 28, that participates in a SN2’ reaction with the solvent, yielding 20i.

The reactivity of heterocyclic substrates was also examined. When compound 3j was treated with HTIB, the ring expansion reaction also took place. However, an inseparable mixture of seven-membered ring O-heterocycles 5j, 8j, and 14j was isolated (Table 2, Entry 10). The oxygen at the ortho position of the migrating carbon 8j change the reactivity, as observed in other oxidative rearrangements promoted by iodine(III) [50]. Treatment of the sulfur derivative 3k with HTIB gave exclusively the sulfoxide, in 75% yield (Table 2, entry 11). The first reaction is the oxidation of the sulfide moiety to the corresponding sulfoxide [51]. This electron-withdrawing group would decrease the migratory aptitude of the migrating carbon and the SN2’ reaction became the favorable pathway. The reaction of substrate 3l with HTIB furnished the benzazepine 8l in good yield (Table 2, Entry 12). Structures like 8l are present in many natural products [52] and have different biological activities [53–56], being important building blocks for drugs. Among the methodologies for the preparation of benzazepines [57–62], metals are involved in most of them and a metal free approach could be a useful alternative, specially for pharmaceuticals applications.
The antiproliferative activity of seven-membered rings products (5f + 8f, 8d, 8g, 12f and 8l) was evaluated against a panel of nine human tumor cell lines and one immortalized human cell line using a protocol described in the literature [63,64]. This methodology aims to evaluate a group of samples in many different tumor cell lines to find evidence of their antiproliferative profile. In order to prioritize further evaluations, a threshold for mean logTGI (Total Growth Inhibition) values (mean log TGI ≤ 1.50) was assumed [65].

Compounds 5f + 8f, 8g and 8l can be classified as inactive considering the average antiproliferative effect (mean logTGI > 1.50) (Table 3). The mixture 5f + 8f (1:1) showed a selective growth inhibitory effect against glioma (U251, TGI = 4.8 µg·mL⁻¹) and prostate (PC-3, TGI = 3.6 µg·mL⁻¹) cell lines. Moreover, compounds 12f and 8d showed, respectively, a moderate (mean logTGI = 1.03) and a weak (mean logTGI = 1.35) cytostatic effects. This suggests that the presence of methoxy groups in the ring fused to the seven-membered system can contribute to the antiproliferative activity and the inclusion of a methoxy group on the carbon of the ring fusion can increase this effect.

Table 3. Antiproliferative activities (TGI, µg·mL⁻¹) of ring expansion products a.

|                  | Doxorubicin | 5f and 8f (1:1) | 8d | 8g | 8l | 12f |
|------------------|-------------|----------------|-----|-----|-----|-----|
| U251             | 0.20        | 4.8            | 8.2 | 43.2| 50.7| 5.2 |
| UACC-62          | 0.86        | 18.1           | 34.4| 59.3| 91.3| 8.4 |
| MCF-7            | 1.2         | 14.0           | 25.9| 52.8| 70.1| 6.0 |
| NCI-ADR/RES      | 3.5         | 19.8           | 42.0| 57.9| 79.9| 6.5 |
| 786-0            | 0.27        | 15.9           | 27.6| 72.8| 102.4|6.7 |
| NCI-H460         | 0.61        | 37.2           | 60.3| 64.6| 157.7|22.9|
| PC-3             | 0.74        | 3.6            | 8.5 | 44.8| 88.5| 10.6|
| HT29             | 11.4        | 17.5           | 24.4| 55.7| 124.6|34.6|
| K562             | 0.96        | >250           | 25.6| >250| 167.6|46.3|
| HaCat            | 0.16        | 7.5            | 11.8| 48.1| 206.0|4.1 |
| Mean LogTGI      | −0.081      | >1.2           | 1.35| >1.8| 2.02| 1.03|

a Tumor human cell lines: U251 (glioma); UACC-62 (melanoma); MCF-7 (breast); NCI-ADR/RES (ovarian resistant to multiple drugs); 786-0 (kidney); NCI-H460 (lung, non small cells); PC-3 (prostate); HT29 (colon); K562 (leukemia). Immortalized non-tumoral cell line: HaCat (human keratinocyte).

3. Experimental Section

General Information

HTIB, HMDS and MeOH were used as received. THF (tetrahydrofuran) was freshly distilled from sodium/benzophenone, CH₂Cl₂ was distilled from CaH₂ and stored with molecular sieves 3 Å. Vinyl magnesium bromide was purchased from Aldrich or prepared from vinyl bromide and magnesium turnings [66]. 1-Tetralone was distilled before used (bp: ~155 °C, 32 mmHg). Column chromatography was performed using silica gel 200–400 Mesh. TLC analyses were performed in silica gel 60 F₂₅₄ plates, using UV, I₂, p-anisaldehyde, or phosphomolybdic acid solution for visualization. ¹H- and
13C-NMR spectra were recorded on Bruker (Billerica, MA, USA) or Varian spectrometers (Palo Alto, CA, USA). IR spectra were measured on a Perkin-Elmer 1750-FT (Waltham, MA, USA). Gas chromatography analyses were performed in a HP-6890 series II (Agilent, Santa Clara, CA, USA) and/or Shimadzu-2010 (Kyoto, Japan). Melting points were done in Büchi Melting Point B-545 (Flawil, Switzerland) and are uncorrected. HRMS analyses were performed on a Bruker Daltonics Microtof Eletrospray (Billerica, MA, USA). CHN analyses were performed with Perkin-Elmer CHN 2400 equipment (Waltham, MA, USA). The percentage of bromine in the organic compounds was determined by volumetric titration using a solution of Hg(NO3)2 and diphenylcarbazone as indicator. The tests with KI paper were performed applying a drop of the reaction mixture in a filter paper previously impregnated with a solution of KI (10%), which was dried at 100 °C. The preparation of compounds 3b–c and 3h–k was reported in the previous communication [34].

1-Tosyl-2,3-dihydroquinolin-4(1H)-one (11). To a mixture of 1,2,3,4-tetrahydroquinoline (3.7 mL, 4.0 g, 30 mmol) in anhydrous pyridine (15 mL), was added TsCl (7.63 g, 40.0 mmol, 1.3 equiv) at rt. The mixture was stirred at 60 °C for 15.5 h. The temperature was increased to 110 °C and the mixture was stirred for 5.5 h. The reaction mixture was cooled to −5 °C and hot H2O (25 mL) was added, precipitating the crude product, which was filter under reduced pressure. The solid was washed with HCl (0.01 mol·L−1) and H2O, and dried in the air. The small and brownish crystals (9.808 g) were recrystallized with MeOH (200 mL), giving colorless crystals of 1-tosyl-1,2,3,4-tetrahydroquinoline [67] (7.15 g, 24.9 mmol, 83%). mp: 94.6–95.2 °C (lit.[67]: 91–92 °C).To a solution of 1-tosyl-1,2,3,4-tetrahydroquinoline (1.56 g, 5.00 mmol) in acetone (22.5 mL) at 0 °C was added anhydrous MgSO4 (1.51 g, 12.5 mmol, 2.5 equiv) and H2O (9.0 mL). Subsequently, KMnO4 (4.35 g, 27.5 mmol, 5.5 equiv) was added dropwise for 30 min. The mixture was stirred for 27 h at rt. The solid was filtered under reduced pressure, washed with CH2Cl2 and H2O. Saturated solution of K2S2O5 (50 mL) was added to the resulting solution. The solid was filtered under reduced pressure. The solution was extracted with CH2Cl2, washed with brine, and dried with anhydrous MgSO4. The solvent was removed under reduced pressure, giving 11 [68], as white crystals (1.18 g, 3.93 mmol, 79%). mp 141.1–141.9 °C (lit. [69] 141–142 °C).

5-Methoxy-1-vinyl-1,2,3,4-tetrahydro naphthalen-1-ol (2d). General Procedure for the Preparation of Allylic Alcohols. To a solution of 5-methoxy-1-tetralone (3.52 g, 20.0 mmol) in anhydrous THF (20 mL) in a Schlenk flask, was added CH2=CHMgBr in THF (1 mol·L−1, 50.0 mL, 50.0 mmol) at 0 °C. The mixture was stirred for 3–4 h at rt. Saturated solution of NH4Cl (32 mL) was added dropwise at 0 °C. The aqueous phase extracted with AcOEt, dried under anhydrous MgSO4, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (hexanes/AcOEt, 4:1), giving 2d (2.97 g, 14.6 mmol, 73%), as colorless oil. IR (film) ν/cm−1 1257, 1467, 1583, 2938, 3430; 1H-NMR (300 MHz, CDCl3) δ 1.79–1.98 (m, 5H), 2.53–2.83 (m, 2H), 3.82 (s, 3H), 5.19 (dd, 1H, J = 1.7, 10.8), 5.29 (dd, 1H, J = 1.7, 17.1), 6.04 (dd, 1H, J = 10.8, 17.1), 6.75 (dd, 1H, J = 0.9, 8.1), 7.00–7.03 (m, 1H), 7.17 (t, 1H, J = 8.1); 13C-NMR (75 MHz, CDCl3) δ 18.5, 23.2, 37.3, 55.4, 73.3, 108.5, 113.1, 119.7, 126.2, 126.4, 141.0, 144.8, 156.9; LRMS m/z (%) 63 (18), 115 (98), 128 (54), 141 (58), 155 (65), 171 (55), 186 (100); HRMS (ESI) m/z, calcd for [C13H16O2+Na]⁺ 227.1048, found: 227.1039.
((5-Methoxy-1-vinyl-1,2,3,4-tetrahydronaphthalen-1-yl)oxy)trimethylsilane (3d). General Procedure for the Protection with a TMS group. A solution of 2d (2.86 g, 14.0 mmol), I₂ (a crystal) in anhydrous CH₂Cl₂ (56 mL) was added dropwise for 5 min to a solution of HMDS (2.4 mL, 11 mmol) in anhydrous CH₂Cl₂ (14 mL). This mixture was stirred for 30 min at rt and Na₂S₂O₃ (4.2 g) was added. The mixture became clear and was stirred for 30 min. The mixture was filtered through a silica pad (5 × 2 cm) using CH₂Cl₂ as eluent. The solvent was removed under reduced pressure and the product was purified by flash column chromatography (hexanes/AcOEt, 17:3), giving 3d (1.60 g, 5.79 mmol, 41%) as a slightly yellow oil. IR (film) ν/cm⁻¹ 1837, 1046, 1257, 1457, 1584, 2941; ¹H-NMR (300 MHz, CDCl₃) δ -0.04 (s, 9H), 1.70–1.85 (m, 1H), 1.87–1.99 (m, 3H), 2.56–2.78 (m, 2H), 3.81 (s, 3H), 5.05 (dd, 1H, J = 1.8, 16.8), 5.09 (dd, 1H, J = 1.8, 10.5), 6.04 (dd, 1H, J = 10.5, 16.8), 6.71 (dd, 1H, J = 1.2, 7.8), 7.04 (dd, 1H, J = 10.5, 16.8), 6.71 (dd, 1H, J = 1.2, 7.8), 7.04 (dd, 1H, J = 1.2, 7.8), 7.13 (t, 1H, J = 7.8); ¹³C-NMR (75 MHz, CDCl₃) δ 2.2, 18.9, 23.0, 37.4, 55.3, 76.4, 108.1, 113.0, 120.9, 125.7, 126.1, 141.4, 145.7, 156.6; LRMS m/z (%) 73 (100), 115 (21), 128 (17), 158 (34), 171 (17), 186 (54), 276 (M⁺, 11), 248 (40); HRMS (ESI) m/z, calcd for [C₁₆H₂₄O₂Si+Na]⁺: 299.1445, found: 299.1442.

((6,7-Dimethoxy-1-vinyl-1,2,3,4-tetrahydronaphthalen-1-yl)oxy)trimethylsilane (3f). The general procedure was followed using 6,7-dimethoxy-1-tetralone (2.12 g, 10.0 mmol), THF (17 mL), and CH₂=CHMgBr (1 M in THF, 27.2 mL, 27.2 mmol). A solution of the crude product (2.69 g) in anhydrous CH₂Cl₂ (10 mL) was added dropwise for 5 min to a solution of HMDS (1.7 mL, 8.4 mmol) and of I₂ (a crystal) in anhydrous CH₂Cl₂ (40 mL). This mixture was stirred for 30 min at rt and Na₂S₂O₃ (3.11 g) was added. The mixture became clear and was stirred for 30 min. The mixture was filtered through a silica pad (5 × 2 cm) using hexanes/Et₂O (97:3) as eluent. The solvent was removed under reduced pressure and the product was purified by flash column chromatography (hexanes/AcOEt, 17:3), giving 3f, as a white solid (1.81 g, 5.91 mmol, 59%). mp 48.5–49.7 °C; IR (film) ν/cm⁻¹ 1840, 910, 928, 1032, 1049, 1116, 1137, 1216, 1462, 1516, 2952, 3001; ¹H-NMR (300 MHz, CDCl₃) δ -0.03 (s, 9H), 1.71–1.84 (m, 1H), 1.87–2.01 (m, 3H), 2.62–2.79 (m, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 5.06 (dd, 1H, J = 1.8, 16.8), 6.02 (dd, 1H, J = 10.5, 16.8), 6.52 (s, 1H), 6.89 (s, 1H); ¹³C-NMR (75 MHz, CDCl₃) δ 2.2, 19.8, 29.1, 38.0, 55.7 (2C), 76.4, 110.7, 111.5, 112.9, 129.4, 132.0, 145.8, 146.8, 148.1; anal. calcd for C₁₇H₂₆O₃Si: C, 66.62; H, 8.55, found: C, 67.03; H, 8.69 (% H); LRMS m/z (%) 45 (41), 73 (100), 115 (21), 128 (16), 186 (16), 216 (17), 179 (39), 306 (M⁺, 6); HRMS (ESI) m/z, calcd for [C₁₇H₂₆O₃Si+Na]⁺: 329.1549, found: 329.1552.

((5-Bromo-1-vinyl-1,2,3,4-tetrahydronaphthalen-1-yl)oxy)trimethylsilane (3g). The general procedure was followed using 5-bromo-1-tetralone (0.788 g, 3.50 mmol), THF (25 mL), and CH₂=CHMgBr (1 M in THF, 8.8 mL, 8.8 mmol, 2.5 equiv). The crude product was protected with a TMS group following the general procedure, but using HMDS (0.7 mL, 3.2 mmol) in CH₂Cl₂ (16 mL). The mixture was filtered through a silica pad (5 × 2 cm) using hexanes/Et₂O (97:3) as eluent. The solvent was removed under reduced pressure and the product was purified by flash column chromatography (hexanes/AcOEt, 17:3), giving 3g (0.783 g, 2.50 mmol, 71%), as slightly yellow oil. IR (film) ν/cm⁻¹ 756, 840, 900, 915, 1048, 1251, 2948; ¹H-NMR (300 MHz, CDCl₃) δ -0.02 (s, 9H), 1.77–1.86 (m, 1H), 1.89–2.01 (m, 3H), 2.67–2.82 (m, 2H), 4.99 (dd, 1H, J = 1.5, 17.1), 5.12 (dd, 1H, J = 1.5, 10.5), 6.02 (dd, 1H, J = 10.5, 17.1), 7.03 (t, 1H, J = 7.8), 7.40 (dd, 1H, J = 1.2, 7.8), 7.44 (dd, 1H, J = 1.2, 7.8); ¹³C-NMR (75 MHz, CDCl₃) δ 2.2, 19.2, 30.3, 37.1, 77.2, 113.9,
124.9, 126.7, 128.1, 131.3, 136.4, 143.0, 145.3; anal. calcd for C\textsubscript{15}H\textsubscript{21}BrOSi: C, 55.38; H, 6.51; Br, 24.56; found: C, 55.61; H, 6.55; Br, 24.67; LRMS \textit{m/z} (%) 45 (33), 73 (100), 115 (21), 128 (21), 155 (34), 296/298 (26), 326/324 (M\textsuperscript{++}, 6).

\textit{1-Tosyl-4-((trimethylsilyl)oxy)-4-vinyl-1,2,3,4-tetrahydroquinoline (3l)}. The general procedure was followed using 1l (2.41 g, 8.00 mmol), THF (25 mL), and CH\textsubscript{2}=CHMgBr (1 M in THF, 20.0 mL, 20.0 mmol, 2.5 equiv). The crude alcohol was purified by flash column chromatography (CH\textsubscript{2}Cl\textsubscript{2} as eluent), giving the alcohol (0.631 g, 2.00 mmol, 25%), as yellow oil. The alcohol was protected following the general procedure, but using HMDS (0.34 mL, 1.6 mmol, 0.8 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (2 mL) and a solution of the alcohol (0.631 g, 2.00 mmol) and I\textsubscript{2} (a crystal) in CH\textsubscript{2}Cl\textsubscript{2} (8 mL). Compound 3l (0.800 g, 1.99 mmol, 100%) was obtained as brown oil. IR (film) \nu/cm\textsuperscript{−1} 1840, 1166, 1357, 2957; \textit{1H-NMR} (300 MHz, CDCl\textsubscript{3}) \delta −0.13 (s, 9H), 1.64–1.82 (m, 2H), 2.37 (s, 3H), 3.86–4.01 (m, 2H), 4.89 (dd, 1H, \textit{J} = 1.5, 16.8), 5.00 (dd, 1H, \textit{J} = 1.5, 10.5), 5.66 (dd, 1H, \textit{J} = 10.5, 16.8), 7.08 (td, 1H, \textit{J} = 1.2, 7.5, 11.7), 7.19–7.22 (m, 2H), 7.23–7.27 (m, 1H), 7.32 (dd, 1H, \textit{J} = 1.8, 11.7), 7.55 (dt, 2H, \textit{J} = 1.8, 8.4), 7.87 (dd, 1H, \textit{J} = 0.9, 8.4); \textit{13C-NMR} (75 MHz, CDCl\textsubscript{3}) \delta 2.2, 21.5, 35.2, 43.4, 73.8, 114.4, 122.6, 124.1, 127.2 (2C), 128.3, 129.4, 129.6 (2C), 131.8, 136.1, 136.7, 143.7, 143.8; LRMS \textit{m/z} (%) 45 (10), 73 (54), 91 (27), 130 (20), 155 (100), 218 (9), 246 (18), 401 (M\textsuperscript{++}, 3); HRMS (ESI) \textit{m/z}, calcd for [C\textsubscript{21}H\textsubscript{27}NO\textsubscript{3}SSi+Na]\textsuperscript{+}: 424.1379, found: 424.1376.

\textit{1,5-Dimethoxy-5-(methoxymethyl)-5,7,8,9-tetrahydro-6H-benzo[7]annulen-6-one (8d)}. General Procedure for the Ring Expansion of TMS-protected Allylic Alcohols. To a solution of 3d (0.138 g, 0.500 mmol) in MeOH (2 mL) was added HTIB (0.490 g, 1.25 mmol) at 0 °C. The progress of the reaction was monitored by filter paper impregnated with a solution of KI (10%). The reaction was stirred for 1 h at this temperature and 1 h at rt. The reaction was quenched with saturated solution of NaHCO\textsubscript{3} (3 mL). The aqueous phase was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 5 mL). The organic phase was washed with H\textsubscript{2}O and with brine. The organic phase was purified by flash column chromatography (hexanes/Et\textsubscript{2}O, 2:3), giving 8d (0.0676 g, 0.256 mmol, 51%), as yellow oil. IR (film) \nu/cm\textsuperscript{−1} 11079, 1098, 1469, 1581, 1718, 2834, 2935; \textit{1H-NMR} (300 MHz, CDCl\textsubscript{3}) \delta −0.13 (s, 9H), 1.67–1.82 (m, 1H), 2.06–2.18 (m, 1H), 2.40–2.47 (m, 1H), 2.47–2.52 (m, 1H), 2.76 (s, 3H), 2.96 (dd, 1H, \textit{J} = 3.3, 13.2), 3.19 (s, 3H), 3.34–3.20 (m, 2H), 3.39 (s, 3H), 3.81 (s, 3H), 3.98 (d, 1H, \textit{J} = 9.6), 4.21 (d, 1H, \textit{J} = 9.6), 6.83–6.89 (m, 2H), 7.19 (t, 1H, \textit{J} = 8.1); \textit{13C-NMR} (75 MHz, CDCl\textsubscript{3}) \delta 21.6, 27.5, 39.5, 51.2, 55.9, 59.7, 72.4, 87.6, 111.3, 119.3, 127.0, 129.9, 136.2, 157.0, 210.1; LRMS \textit{m/z} (%) 45 (56), 77 (22), 91 (29), 115 (25), 144 (41), 159 (61), 172 (37), 191 (100), 219 (36), 264 (M\textsuperscript{++}, 5); HRMS (ESI) \textit{m/z}, calcd for [C\textsubscript{15}H\textsubscript{20}O\textsubscript{4}+Na]\textsuperscript{+}: 287.1259, found: 287.1258.

\textit{Oxidation of 3f with HTIB}. The general procedure for ring expansion was followed, using HTIB (0.490 g, 1.25 mmol), solution of 3f (0.153 g, 0.500 mmol) and of PTSA (0.020 g, 0.12 mmol, 20 mol %) in AcOEt/MeOH (2:1, 3 mL) at −72 °C. The residue was purified by flash column chromatography (hexanes/AcOEt, 3:7), giving a mixture of 5f and 8f (0.100 g, 0.424 mmol, 76%), as yellow oil and 12f (0.015 g, 0.054 mmol, 10%), as white solid. 2,3-Dimethoxy-5-(methoxymethyl)-5,7,8,9-tetrahydro-6H-benzo[7]annulen-6-one (5f): \textit{1H-NMR} (500 MHz, CDCl\textsubscript{3}) \delta 1.88–1.95 (m, 1H), 2.05–2.11 (m, 1H),
2.54–2.58 (m, 1H), 2.67–2.72 (m, 1H), 2.84–2.94 (m, 2H), 3.38 (s, 3H), 3.83 (dd, 1H, J = 6.0, 9.0), 3.87 (d, 6H, J = 2.0), 4.00–4.02 (m, 1H), 4.12 (dd, 1H, J = 3.5, 6.5, 14.0), 4.19 (s, 3H), 4.20 (d, 1H, J = 9.9), 7.11 (t, 1H, J = 7.8), 7.31 (dd, 1H, J = 1.2, 7.8), 7.57 (dd, 1H, J = 1.2, 7.8); 13C-NMR (125 MHz, CDCl3) δ 28.0, 32.6, 43.5, 55.9, 56.1, 56.6, 59.2, 71.2, 111.5, 113.1, 126.6, 133.0, 147.6, 147.8, 209.3; HRMS (ESI) m/z, calcd for [C15H20O4+Na]+: 287.1259, found: 287.1259.

2,3,5-Trimethoxy-5-(methoxymethyl)-5,7,8,9-tetrahydro-6H-benzo[7]annulen-6-one (8f): 1H-NMR (500 Hz, CDCl3) δ 1.80–1.87 (m, 1H), 2.12–2.19 (m, 1H), 2.44 (quin, 1H, J = 5.5), 2.63 (ddd, 1H, J = 3.5, 6.5, 14.0), 3.19 (s, 3H), 3.24–3.32 (m, 2H), 3.42 (s, 3H), 3.88 (d, 6H, J = 2.0), 3.98 (d, 1H, J = 10.0), 4.20 (d, 1H, J = 9.5), 6.62 (s, 1H), 6.67 (s, 1H); 13C-NMR (125 MHz, CDCl3) δ 28.9, 33.2, 39.4, 51.0, 55.8, 56.1, 59.7, 72.1, 87.5, 110.8, 114.2, 126.3, 134.5, 147.3, 148.6, 209.9; HRMS (ESI) m/z, calcd for [C16H22O5+Na]+: 317.1365, found: 317.1364.

trans-3,4a-Dimethoxy-9-(methoxymethyl)-4a,5,6,7-tetrahydro-2H-benzo[7]annulene-2,8(9H)-dione (12f): mp 160.4–161.0 °C; IR (film) ν/cm⁻¹ 11091, 1170, 1227, 1392, 1451, 1669, 1700, 2937; 1H-NMR (300 MHz, CDCl3) δ 1.46–1.55 (m, 1H), 1.67–1.76 (m, 1H), 2.30–2.60 (m, 4H), 3.62 (dd, 1H, J = 7.2, 9.6), 3.71 (s, 3H), 3.98 (dd, 1H, J = 6.6, 9.6), 4.34 (t, 1H, J = 6.9), 5.64 (s, 1H), 6.23 (d, 1H, J = 0.9); 13C-NMR (75 MHz, CDCl3) δ 17.8, 42.6, 42.9, 50.9, 52.6, 55.1, 59.2, 69.9, 77.4, 118.7, 128.6, 151.7, 158.0, 180.1, 205.1; LRMS m/z (%) 39 (49), 51 (76), 65 (44), 77 (84), 91 (100), 103 (42), 115 (57), 131 (42), 149 (51), 161 (54), 177 (65), 192 (40), 205 (60), 220 (96), 233 (26), 248 (43); HRMS (ESI) m/z, calcd for [C15H20O5+Na]+: 303.1208, found: 303.1207.

5-Methoxy-5-(methoxymethyl)-1-tosyl-1,2,3,5-tetrahydro-4H-benzo[b]azepin-4-one (8l). The reaction was performed as described for 8g, using a solution of 3l (0.197 g, 0.490 mmol) and of PTSA (0.020 g, 0.12 mmol, 24 mol %) in MeOH (3 mL) and HTIB (0.481 g, 1.23 mmol). The residue was purified by flash column chromatography (hexanes/AcOEt/CH2Cl2, 5:1:4), giving 8l (0.135 g, 0.346 mmol, 69%), as slightly yellow solid. mp 100.4–100.7 °C; IR (film) ν/cm⁻¹ 11159, 1348, 1454, 1487, 1720, 2827, 2930; 1H-NMR (300 MHz, CDCl3) δ 2.45 (s, 3H), 2.51–2.58 (m, 1H), 3.06–3.14 (m, 1H), 3.23 (s, 3H), 3.31 (s, 3H), 3.73 (d, 1H, J = 10.8), 3.83 (bs, 2H), 4.19 (d, 1H, J = 10.5), 7.29–7.38 (m, 5H), 7.55–7.57 (m, 5H), 7.64 (s, 1H), 7.71 (d, 1H, J = 7.8), 7.97 (d, 1H, J = 7.8), 8.17 (d, 1H, J = 7.8); 13C-NMR (125 MHz, CDCl3) δ 28.0, 32.6, 43.5, 55.9, 56.1, 56.6, 59.2, 71.2, 111.5, 113.1, 126.6, 133.0, 147.6, 147.8, 209.3; HRMS (ESI) m/z, calcd for [C16H22O5+Na]+: 317.1365, found: 317.1364. 

1-Bromo-5-methoxy-5-(methoxymethyl)-5,7,8,9-tetrahydro-6H-benzo[7]annulen-6-one (8g). To a solution of 3g (0.193 g, 0.481 mmol) and of PTSA (0.020 g, 0.12 mmol, 24 mol %) in MeOH (3 mL) was added HTIB (0.471 g, 1.20 mmol) at 0 °C. The mixture was stirred for 1 h. The temperature was increased to rt and the mixture was stirred for 2 h. The temperature was increased to 50 °C and the mixture was stirred for 3 h. The reaction was quenched with saturated solution of NaHCO₃ (5 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 5 mL). The organic phase was washed with H₂O and with brine. The organic phase was dried with anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (hexanes/AcOEt, 9:1), giving 8g (0.102 g, 0.325 mmol, 65%), as slightly yellow oil. IR (film) ν/cm⁻¹ 1744, 790, 1119, 1437, 1719, 2828, 2932; 1H-NMR (300 MHz, CDCl3) δ 1.78–2.14 (m, 2H), 2.38–2.48 (m, 1H), 2.99–3.14 (m, 1H), 3.21 (s, 3H), 3.24–3.30 (m, 2H), 3.35 (s, 3H), 3.93 (d, 1H, J = 9.6), 4.12 (d, 1H, J = 9.9), 7.11 (t, 1H, J = 7.8), 7.31 (dd, 1H, J = 1.2, 7.8), 7.57 (dd, 1H, J = 1.2, 7.8); 13C-NMR (125 MHz, CDCl3) δ 28.0, 32.6, 43.5, 55.9, 56.1, 56.6, 59.2, 71.2, 111.5, 113.1, 126.6, 133.0, 147.6, 147.8, 209.3; HRMS (ESI) m/z, calcd for [C14H1779BrO3+Na]+: 335.0259, found: 335.0261, calcd for [C14H1781BrO3+Na]+: 337.0238, found: 337.0230.
1H), 7.77 (dt, 2H, J = 1.8, 3.9, 8.4); 13C-NMR (75 MHz, CDCl3) δ 21.6, 38.8, 48.6, 52.5, 59.6, 72.5, 85.4, 127.5, 127.7 (2C), 128.1, 129.3, 129.5, 129.8 (2C), 137.3 (2C), 144.0 (2C), 205.4; LRMS m/z (%): 45 (100), 65 (52), 77 (27), 91 (87), 130 (33), 389 (M+•, 1); HRMS (ESI) m/z, calcd for [C20H23NO5S+Na]+: 412.1195, found: 412.1182.

The compounds 5f + 8f (1:1), 8d, 8g, 12, 15 and 22l were evaluated in vitro against a panel of nine cell lines [U251 (glioma); UACC-62 (melanoma); MCF-7 (breast); NCI-ADR/RES (ovarian resistant to multiple drugs); 786–0 (kidney); NCI-H460 (lung, non small cells); PC-3 (prostate); HT29 (colon); K562 (leukemia)] kindly provided by Frederick MA (National Cancer Institute, Bethesda, MD, USA) and the immortalized human keratinocytes (HaCat) cell line kindly provided by Prof. Dr. Ricardo Della Coletta (University of Campinas, UNICAMP, Campinas, Brazil). Stock and experimental cultures were grown in medium containing 5 mL RPMI 1640 (GIBCO BRL) supplemented with 5% fetal bovine serum (GIBCO BRL). Penicillin/Streptomycin mixture (1000 U·mL−1:1000 µg·mL−1, 1 mL L−1 RPMI) was added to the experimental cultures. Cells in 96-well plates (100 µL cells well−1) were exposed to sample concentrations in DMSO/RPMI (0.25, 2.5, 25, 250 µg·mL−1) in triplicate at 37 °C, 5% of CO2 in air for 48 h. The final DMSO concentration did not affect cell viability. Doxorubicin (0.025 to 25 µg·mL−1) was used as positive control. Before (T0 plate) and after the sample addition (T1 plates), cells were fixed with 50% trichloroacetic acid, and cell proliferation was determined by spectrophotometric quantification (540 nm) of cellular protein using the sulforhodamine B assay. Using the dose-response curve for each cell line, the concentration that totally inhibits cell growth (TGI, expressed in µM) was determined through non-linear regression analysis using ORIGIN software version 8.0 (OriginLab Corporation, Northampton, MA, USA, 2007) [63,70].

4. Conclusions

In conclusion, a metal-free approach for the synthesis of seven- and eight-membered rings through an iodine(III)-mediated ring expansion reaction was described. The substrates can be easily obtained from readily available starting materials. The amount of the oxidizer and the reaction conditions can be managed to obtain different products. Moreover, a short route to the synthesis of medium-ring lactones was developed. The antiproliferative activity of new seven-membered ring compounds was evaluated, and the results showed compound 12f as having a moderated citostatic effect. The results herein described have great potential for application in the chemical synthesis of seven-membered rings.

Supplementary Materials

Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/20/01/1475/s1.

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Author Contributions

The project was conceived by Silva, L.F., Jr. The experiment design concerning the chemical part was realized by Silva, L.F., Jr. and Silva, S.B.L. and the experiments related with the antiproliferative activity were idealized by Torre, A.D.; Carvalho, J.E. and Ruiz, A.L.T.G. The chemical experiments were performed by Silva, S.B.L. and the antiproliferative ones by Torre, A.D. and Ruiz, A.L.T.G. All the authors contributed in the discussion of the results and in the manuscript preparation.

Conflicts of Interest

The authors declare no conflict of interest.

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