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Unique ring expansion of a 6-3 bicyclic ring system forming a functionalized 7-membered ring accelerated by nitrogen functional groups

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ABSTRACT

The treatment of (2-hydroxy-5-oxobicyclo [4.1.0] hept-3-en-3-yl) carbamic acid esters and (2-hydroxy-5-oxobicyclo [4.1.0] hept-3-en-3-yl) benzamide with TMSCl gave 7-membered ring compounds in good yields. The structure of the substituent at the C3 position of the cyclohexene ring is crucial for this ring expansion. The reaction mechanism is thought to involve the formation of a norcaradiene (bicyclo [4.1.0] hept-2,4-diene) structure and subsequent electrocyclic reaction.

Cyclopropane rings easily undergo several types of ring openings under appropriate conditions to afford acyclic or different cyclic molecules and are therefore widely applied in organic synthesis as useful building blocks.[1–4] The ring system has also been found in natural products isolated from various living species.[5–8] Their ring opening frequently correlate with biochemical mechanisms for defense against natural enemies and adaptation to the habitat environment.[9–11] Furthermore, many have potential antibacterial and antitumor activities due to the inherent ring strain. For example, duocarmycin (**4**) is known to undergo alkylation by an adenine residue in DNA through ring opening of the cyclopropane.[12–14] Dehydroxymethyl-epoxyquinomycin (DHMEQ, **6**) is a well known and potent NF-κB inhibitor developed by Umezawa and co-workers (Fig. 1).[15,16] The biological activity is closely related to coupling with a Cys residue in NF-κB, concomitant with ring opening of the epoxide. We previously synthesized a DHMEQ analogue **7** containing a cyclopropane ring with an interest in the biological activity based on opening the small-sized ring.[17] Unfortunately, analogue **7** did not inhibit NF-κB activity contrary to our expectation, but a unique ring expansion attributed to the nature of the cyclopropane ring was observed during the course of the synthetic study. This report describes the ring expansion of a 6-3 bicyclic ring system forming a seven-membered ring accelerated by attendant carbamate or amide functional groups.

What led us to discover this novel ring expansion was an attempt at protecting the hydroxyl group of synthetic intermediate **7a** with a TBS group. Addition of *tert*-butyldimethylsilyl chloride (TBSCl) and triethylamine (Et_3N) to a solution of **7a** in THF did not result in the formation of silylated compound **11**, but rather 7-membered cyclic diketone **8a** and its bicyclic derivative **9** (Table 1, entry 1). Treatment of **7a** with TBSCl and sodium hydride (NaH) in THF generated cyclic carbamate **9** as the major product (Entry 2). The combination of TBSOTf and 2,6-lutidine in CH_2Cl_2 was less suitable for the ring expansion reaction (Entry 3). In order to reveal the essential conditions for ring expansion, bases and silyl reagents were used separately. Treatment of **7a** with only Et_3N or 2,6-lutidine resulted in no reaction (Entries 4 and 5). On the other hand, TBSCl alone caused the ring expansion of **7a** in CH_2Cl_2 to afford **8a** in 51% yield (Entry 6). Furthermore, the reaction proceeded more smoothly to generate **8a** in quantitative yield upon changing the solvent to THF (Entry 7). Since TBSCl behaves like a Lewis acid in this reaction, we examined typical Lewis acids such as $BF_3{\cdot}OEt_2$ and TMSOTf. Treatment of **7a** with TMSOTf in CH_2Cl_2 resulted in the formation of cyclic carbamate **9** along with **10** despite longer reaction times (Entry 8). $BF_3{\cdot}OEt_2$ resulted in formation of the seven-membered products **8a** and **9** (Entry 9). Reagent size seemed to affect the reaction rate; the reaction proceeded more quickly with the use of TMSCl than with the use of TBSCl.

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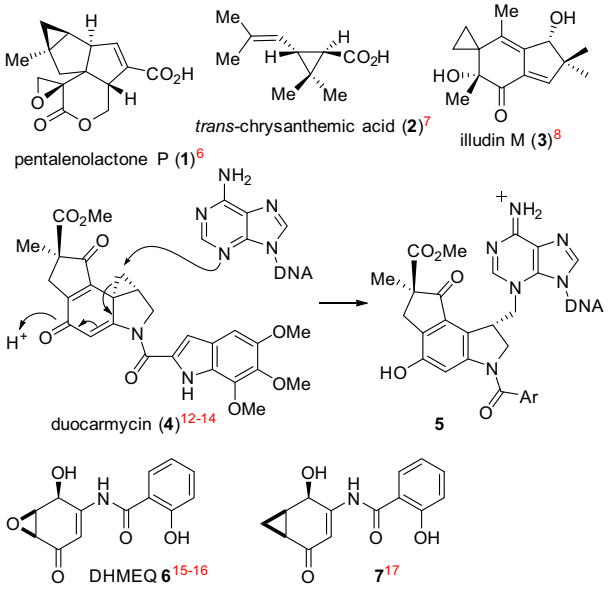


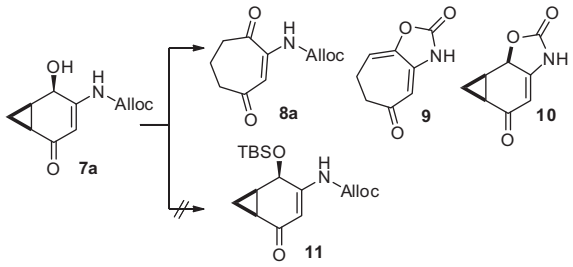
Fig. 1. Compounds possessing a cyclopropane ring.

Notably, **7a** was converted to **8a** within one hour upon treatment of 5 equivalents of TMSCl (Entry 10).

With the optimized conditions in hand, substituents on the cyclohexenone ring were examined for their effect on ring expansion (Table 2). The synthetic route towards substrates **7a-d** is shown in Scheme 1. 2,5-Dimethoxyaniline was protected with each protecting group and oxidized with diacetoxyiodobenzene to give dienones **12a-c**. Treatment of dienones **12a-c** with trimethylsulfoxonium iodide in the presence of NaH resulted in selective cyclopropanation to generate **13a-c**. Deacetalization of **13a-c** with PPTS afforded the diketones **14a-c** in good yields. Finally, reduction of **14a-c** with *L-Selectride*® proceeded stereoselectively to give **7a-c** with a *cis*-configuration. To synthesize benzyl (Bn) derivative **7d**, diketone **14a** was protected with the benzyl group, the allyloxycarbonyl (Alloc) group of compound **15** was then removed with Pd(0) and stereoselective reduction with *L-Selectride*® gave **7d**. Compound **7e** was synthesized following the reported procedure.[18] When the nitrogen atom was protected with an allyloxycarbonyl (Alloc) group or a *t*-butoxycarbonyl (Boc) group, ring expansion smoothly occurred to afford 7-membered ring compounds in good yields (Entries 1 and 2). An amide such as the benzoyl (Bz) group also worked well (Entry 3). On the other hand, the benzyl (Bn) group did not give a 7-membered ring compound (Entry 4). We also examined the substrate with no amine substituent, but it did not induce ring expansion (Entry 5).[18] On the other hand, treatment of **16**, which is a positional isomer of **7a** for the carbamate substituent, under the same conditions resulted in the formation of epimeric alcohol **17** (Scheme 2).

Cleavage of the cyclopropane ring conjugated with a carbonyl group seems at first sight to occur in conjunction with a 1,2-hydride shift (Scheme 3). However, the negative results of **7d-e** remind us of another potential pathway as shown in Scheme 4. TMSCl coordinates with the carbonyl oxygen of **7a-c** to form an iminium ion **A** with the assistance of the electron-releasing nitrogen at the C3 position. Subsequent deprotonation of ion **A**, derived from **7a-c**, results in the formation of enamide **B** with a norcaradiene skeleton,[19] which is thus converted into **8** through an electrocyclic reaction[20] and subsequent keto-enol tautomerization. On the other hand, **7d** should be converted to imine **D**, which does not undergo any further transformation. This can be rationalized by considering that *sec*-enamine-imine tautomerism typically

Table 1
Ring expansion of **7a** under various conditions.[a]



Entry	Reagents (eq.)	Solvent	Time (h)	Yield (%)[b]		
				8a	**9**	**10**
1	TBSCl, Et_3N	THF	1.5	77	12	–
2	TBSCl, NaH	THF	1	11	51	–
3	TBSOTf (2), 2,6-lutidine (4)	CH_2Cl_2	1	–	26	–
4	Et_3N	THF	2.5	No reaction		
5	2,6-lutidine (4)	CH_2Cl_2	2.5	No reaction		
6	TBSCl	CH_2Cl_2	4	51	0	0
7	TBSCl	THF	4	Quant.	0	0
8	TMSOTf	CH_2Cl_2	8	0	20	52
9	BF_3OEt_2	CH_2Cl_2	3	26	52	0
10	TMSCl	THF	1	Quant.	0	0
11	TMSCl (3)	THF	2.5	64	0	0
12	TMSCl (1)	THF	2.5	60	0	0

[a] Reagents and conditions: unless otherwise noted, the reactions were carried out using **7a** (0.1 mmol), reagents (5 equivalents), solvent (0.1 M) at room temperature.
[b] Isolated yields.