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Novel Carbocyle Enlargement in Aqueous Medium

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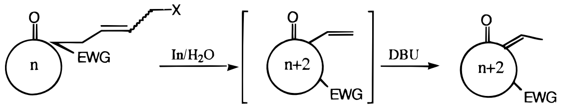
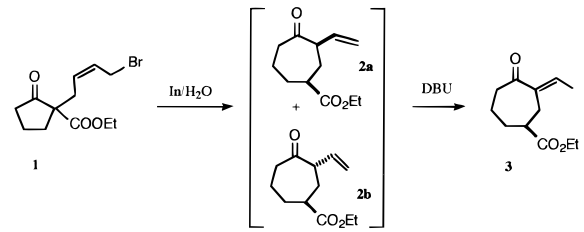
The importance of medium and large size rings in organic chemistry is exemplified by their being the structural core of a large number of biologically important natural products.[1] Among the many methods for medium and large ring synthesis, ring expansion occupies a unique position, inasmuch as the usually disfavored entropy effect associated with medium and large size ring formations can be avoided.[2]

For two-atom ring expansions, the photochemical method of [2 + 2] cyclization−decyclization is the most successful.[3] The [2 + 2] cycloaddition of an acetylenic ester to an enamine of a cyclic ketone and subsequent opening of the annulated cyclobutene moiety formed in another useful method for two-carbon ring expansion.[4] We report here a novel two-atom carbocycle enlargement based on the indium-mediated Barbier−Grignard type reaction in water (eq 1).[5]



(1)

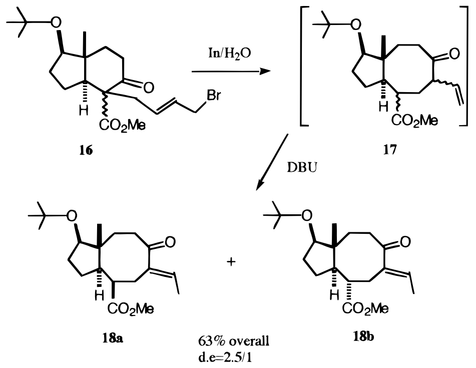
Thus, after cyclopentanone derivative **1** was stirred for 10 h with indium metal powder in water at room temperature, TLC showed the disappearance of the starting material. After workup, the ^{1}H NMR measurement of the crude mixture clearly indicated the presence of two sets of terminal olefins, corresponding to two diastereomers (**2a** and **2b**).[6] Upon treatment with DBU, both sets of terminal olefin signals disappeared and resulted in a single compound **3**. Flash chromatography on silica gel provided an overall yield of 50% of the pure product over two steps. The presence of a quartet peak at 6.8 ppm (integrated to 1 H) and a doublet peak at 1.8 ppm (integrated to 3 H's) in the ^{1}H NMR spectrum of the new compound established the location and geometry of the olefin as indicated. On the other hand, when the initial cyclization was carried out in DMF, a complicated mixture was generated without any recognizable product. No reaction was observed in methanol, with the starting material being recovered completely.



Likewise, 6-, 7-, and 8-membered ring compounds (**4**, **7**, and **10**) were expanded similarly with indium in water to give 8-, 9-, and 10-membered ring products (**5**, **8**, and **11**), respectively (Table 1). In all these cases, only the vinyl type products were initially observed. Subsequent DBU treatment isomerized the olefin to a conjugated system (**6**, **9**, and **12**). Both *cis*- and *trans*-alkyl bromides can be used for the ring expansions. In all cases, the substrates are not water-soluble. However, under a fast-stirring condition, the phase separation does not prevent the proceeding of the reaction.

A cyclododecanone derivative **13** underwent a similar transformation to give a 14-membered ring product **15**.

Ring expansion proceeded equally well in a more complicated system. Reaction of bicyclic compound **16** with indium metal in water generated two sets of diastereomers (**17**), which were transformed to a 2.5/1 mixture of diastereomers (**18a** and **18b**) upon DBU treatment in 63% isolated overall yield over two steps. X-ray crystal analysis shows the major diastereomer



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† To whom correspondence should be made regarding X-ray analysis.

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[6] A typical experimental procedure in as follows: To a mixture of **1** (289 mg, 1 mmol) in 10 mL of aqueous 0.1 N HCl/methanol (3:1) was added indium powder (230 mg, 2 mmol). The reaction mixture was vigorously stirred at room temperature for 10 h, quenched with 1 N HCl (1 mL) aqueous solution, extracted with 10 mL of ether (3×). The combined organic phases were dried over magnesium suflate and concentrated. The residue was then mixed with DBU (304 mg, 2 mmol) in 10 mL THF. The mixture was stirred overnight at room temperature. Workup followed by column chromatography on silica gel provided **3** (105.6 mg, overall yield 50%).

[7] X-ray data for **18a**: $C_{20}H_{32}O_4$; fw = 336.58; orthorhombic; space group $P2_12_12_1$; a = 5.8808(3) Å, b = 17.976(2) Å, c = 18.214(2) Å; V = 1901.8(5) Å^3; Z = 4; R = 0.043, R_w = 0.060, GOF = 2.01 for 1475 observations with $I \geq 3\sigma(I)$.

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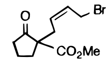
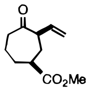
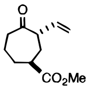
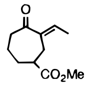
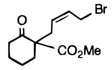
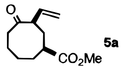
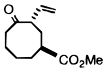
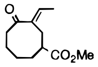
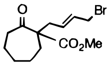
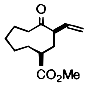
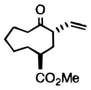
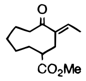
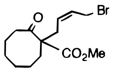
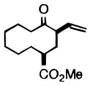
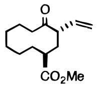
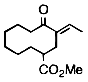
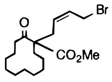
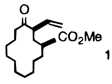
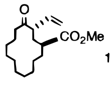
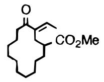
Table 1. Novel Two-Atom Ring Expansion to Medium and Large Rings

Entry	Substrate	Intermediates	Product	Overall Yield
1	 **1**	 **2a** +  **2b**	 **3**	50
2	 **4**	 **5a** +  **5b**	 **6**	51
3	 **7**	 **8a** +  **8b**	 **9**	71
4	 **10**	 **11a** +  **11b**	 **12**	50
5	 **13**	 **14a** +  **14b**	 **15**	49

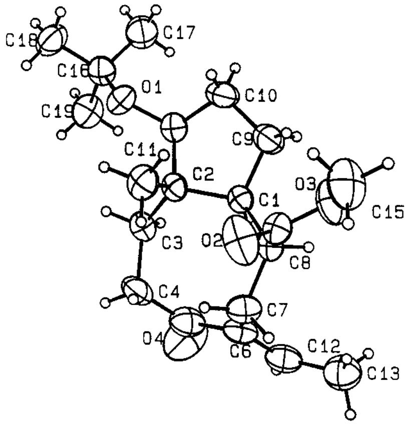


Figure 1. Perspective view of **18a**. Thermal ellipsoids are drawn at the 50% probability level except for hydrogen atoms which are arbitrarily small for clarity.

corresponding to structure **18a** in which all three substituents (*tert*-butoxyl, methyl, and carboxylate) are *cis*-related (Figure 1).[7] Application of the current carbocycle-enlargement method to natural product synthesis is presently being undertaken.

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Supporting Information Available: IR, ^{1}H and ^{13}C NMR, and HRMS data for **3**, **6**, **9**, **12**, **15**, and **18a**; X-ray crystal data for **18a** (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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