Cycloaddition

DOI: 10.1002/ange.201410806

# Type II Intramolecular [5+2] Cycloaddition: Facile Synthesis of Highly Functionalized Bridged Ring Systems**

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*Dedicated to Professor Zhen Yang and Professor Phil S. Baran*

***Abstract:*** *A type II intramolecular oxidopyrylium-mediated [5+2] cycloaddition reaction allows the efficient and diastereoselective formation of various highly functionalized and synthetically challenging bridged seven-membered ring systems (such as bicyclo[4.4.1]undecane, bicyclo[4.3.1]decane, bicyclo[5.4.1]dodecane, and bicyclo[6.4.1]]tridecane). This simple, thermal, direct transformation has a broad substrate scope and is high yielding, with high functional-group tolerance and unique endo selectivity. The highly strained tricyclic cores of ingenol mebutate (picato) and cyclocitrinol are synthesized efficiently and diastereoselectively using this methodology.*

The development of efficient reactions for the synthesis of bridged ring systems is a long-standing challenge, but very significant in organic chemistry, considering that this motif is ubiquitous in natural products with significant biological activities (such as taxol). In particular, bridged seven-membered-ring systems are found in various pharmaceuticals and natural products, such as ingenol (**1**),[1] *N*-methylwelwitindolinone C isothiocyanate (**2**),[2] ajmaline (**3**),[3] and cyclocitrinol (**4**)[4] (Figure 1). Ajmaline is a class Ia antiarrhythmic drug for acute intravenous treatments.[5] Ingenol mebutate (picato; Figure 1) was recently approved by the FDA as a first-in-class drug for the topical treatment of actinic keratosis, a precancerous skin condition.[6] Consequently, some elegant synthetic strategies for the formation of bridged seven-membered-ring systems have been developed,[1g,h,2e] including rearrangement,[1d,f,4f] fragmentation,[1c,4e] ring-closing metathesis,[1e] and intramolecular cyclizations.[2c,d,3c] However, so far no general reactions are available for the direct and efficient synthesis of bridged cycloheptane bicyclic systems.

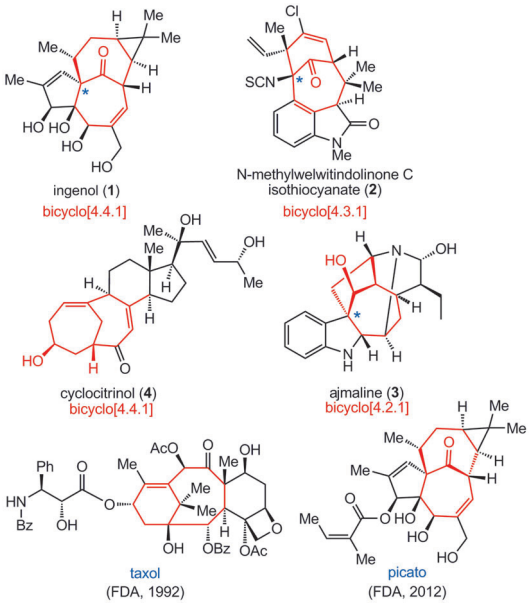


***Figure 1.*** Challenging bridged ring systems.

Natural products with highly functionalized fused seven-membered rings, apart from bridged seven-membered rings, can be formed directly using a type I intramolecular [5+2] cycloaddition[7–9] (e.g. tethered at the 6-position or 2-position of the acetoxypyranone, and tethered at the β-position of the vinylcyclopropane; Scheme 1 A). In 1978, Shea reported a type II intramolecular Diels–Alder (IMDA) reaction (tether is attached to the 2-position of the diene) for the preparation of strained bridged bicyclic six-membered rings[10] (Scheme 1 B). However, only limited skeletons can be synthesized through type II IMDA reactions, which have occasionally been restricted to the gas phase,[11] because of the formation of an unfavorable $sp^2$ carbon atom at the bridgehead position. Particularly, the enantioselective formation of quaternary stereocenters through type II IMDA reactions is rarely reported and still a challenging issue.[12] Stimulated by these studies, particularly by the challenging type II IMDA reaction and our recent work on dearomative indole [5+2] cycloaddition reactions,[13] we speculated whether a type II

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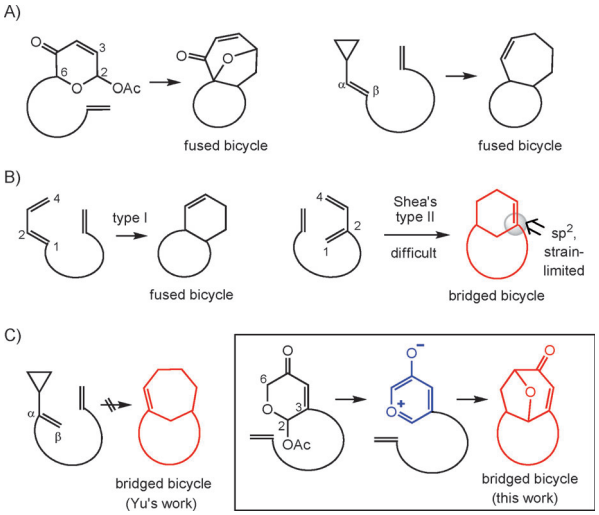
[**] This work was supported by the Natural Science Foundation of China (Grant numbers 21172009, 21402083, and 21472081), the Natural Science Foundation of Guangdong (Grant number S2012010010611) and the Shenzhen Basic Research Program (Grant number JCYJ20130329180259934). We would also like to thank Dr. Tao Wang at PKUSZ for his help with the X-ray crystallographic analysis.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201410806.

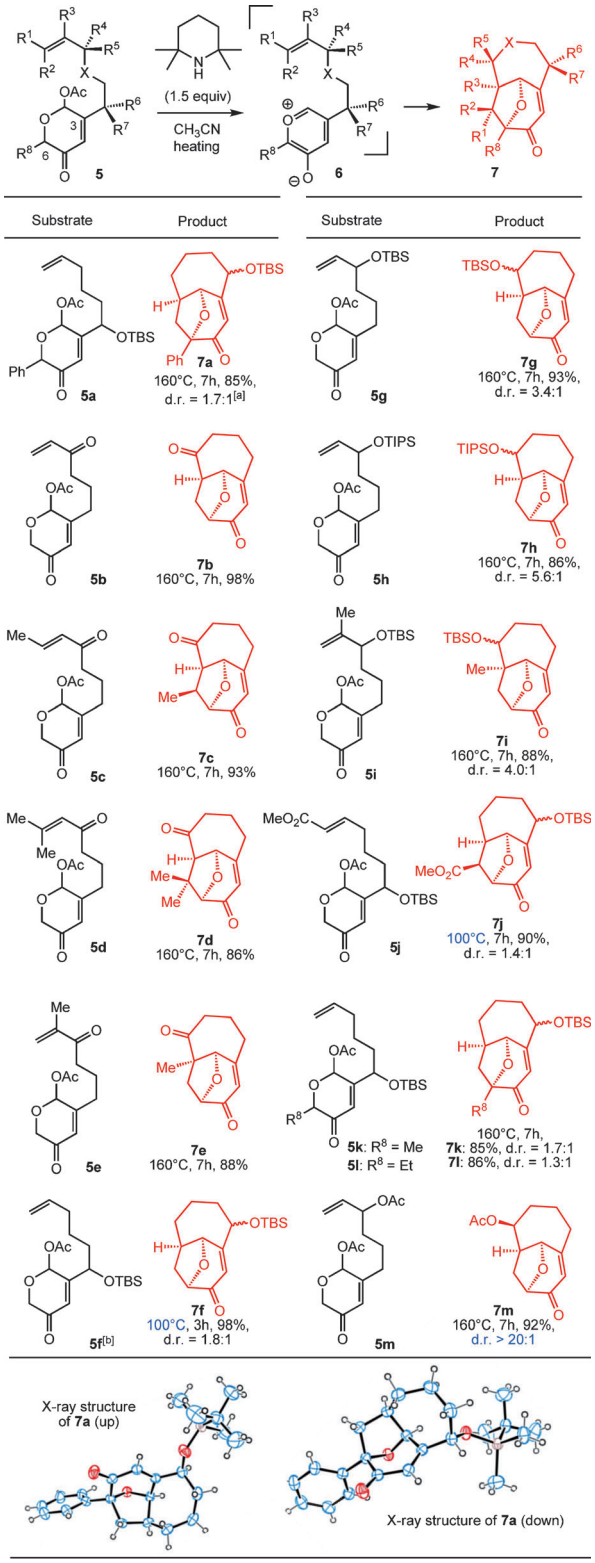
  




***Scheme 1.*** A) Type I intramolecular [5+2] cycloaddition reactions. B) Type I and type II IMDA reaction. C) Type II intramolecular [5+2] cycloaddition to bridged cycloheptane bicycles.

intramolecular [5+2] cycloaddition[14] could be achieved using a new type of substrate, that is, an acetoxypyranone and a dienophile that is tethered at the C3 position of the acetoxypyranone (Scheme 1 C). The anticipated type II intramolecular [5+2] reaction would afford a straightforward method for forming synthetically challenging bridged cycloheptane bicycles (e.g. bicyclo[4.4.1]undecane, bicyclo[4.3.1]decane, and bicyclo[4.2.1]nonane; Figure 1). To the best of our knowledge, there are no reports of type II intramolecular [5+2] cycloaddition reactions. The activation free energy of the type II intramolecular [5+2] cycloaddition would be higher than that of the type I reaction, because of the strain inherent in the formation of an unfavorable bridgehead double bond; this makes Yu's type II intramolecular Rh-catalyzed [5+2] cycloaddition more difficult to achieve, even with longer tethers.[14] Furthermore, the transition-metal-catalyzed [5+2] cycloadditions[9] with an all-carbon tether to form medium-sized rings has been shown to rely on the Thorpe–Ingold effect.[15] But, it was envisaged that the oxidopyrylium ylide[16] (blue in Scheme 1 C) derived from the acetoxypyranone will be more reactive than the electronically neutral vinylcyclopropane; a type II intramolecular oxidopyrylium-mediated [5+2] dipolar cycloaddition reaction would proceed readily under mild conditions as soon as the ylide is formed.[13,17] This will be a unique and novel strategy to access bridged ring systems[18] with a bridgehead double bond, such as cyclocitrinol (**4**). Herein, we report an unusual and general type II intramolecular [5+2] cycloaddition reaction with an oxidopyrylium ylide and a simple alkene. This straightforward transformation afforded a series of bridged seven-membered bicyclic skeletons and allowed the stereoselective synthesis of the highly strained tricyclic cores of ingenol and cyclocitrinol.

First, we prepared acetoxypyranone **5a** (see the Supporting Information), which is an important precursor for oxidopyrylium ylide **6a** (Scheme 2). The type II intramolecular [5+2] cycloaddition reaction was then investigated and




***Scheme 2.*** Substrate scope of the type II intramolecular [5+2] cycloaddition. [a] For X-ray structures, see bottom of the graphic. [b] On a 1.0 gram scale.

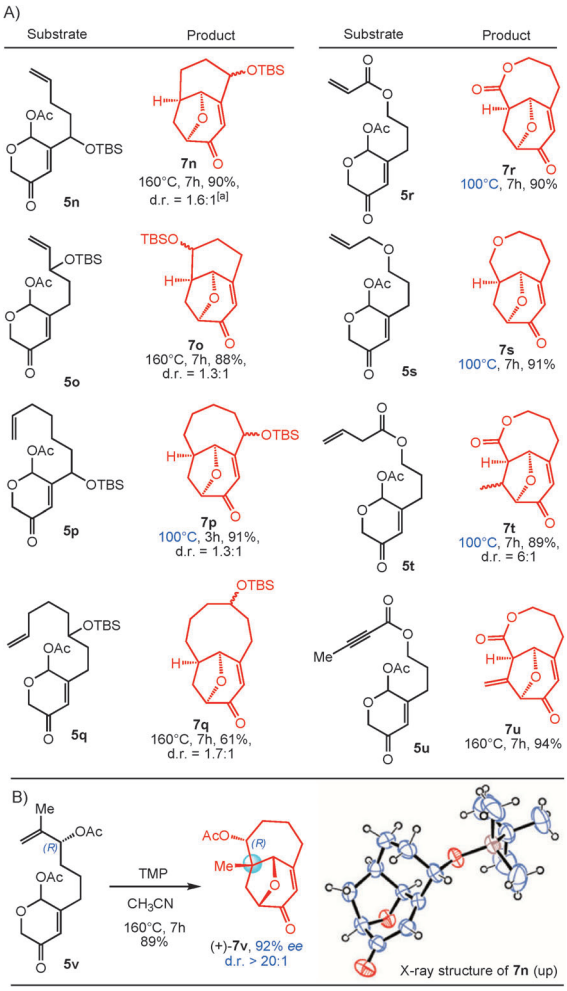
the reaction conditions optimized (Supporting Information). At 160 °C in a sealed tube and using 1.5 equivalents of 2,2,6,6-tetramethylpiperidine (TMP)[19] as the base, **7a** was obtained

in 85% yield as a mixture of diastereoisomers (1.7:1 d.r.). The structures of these isomers were unambiguously confirmed using X-ray crystallography and confirm that the reaction proceeded with exclusive *endo* selectivity.

The scope of this type II intramolecular [5+2] cycloaddition was then explored (Scheme 2). The reaction proceeded well with various acetoxypyranones with an alkene tethered at the C3 position, giving bicyclo[4.4.1]undecanes (**7b–e**) as the sole products, even with the challenging *gem*-dimethyl group (**7d**). The reaction of **5f** at 100 °C for 3 h gave **7f** in 98% yield (1.0 gram scale) as a mixture of diastereoisomers (1.8:1 d.r.). Introduction of an OTBS or OTIPS group at the allylic position of the dienophile improved the diastereoselectivity (3.4:1 and 5.6:1 d.r., respectively), giving bicyclo[4.4.1]undecanes **7g** and **7h**, respectively, in high yield. The presence of a methyl group at the internal carbon center on the alkene, as in **5e** and **5i**, gave high yields of the bridged cycloheptane bicycles **7e** and **7i**, respectively, which have a bridgehead quaternary carbon center. This result is particularly significant because the introduction of a quaternary stereogenic bridgehead carbon center within a bridged bicycle is very challenging. This result offers the possibility to further modify this position (C* in Figure 1) in natural products, such as ingenol, welwitindolinone alkaloids, and ajmaline. Product **7j** was also isolated in 90% yield, showing that an ester at the terminal position of the alkene is also tolerated, and four new stereogenic centers can be introduced diastereoselectively in a single step. Furthermore, these conditions worked well with methyl or ethyl substituents at the C6 position of the acetoxypyranone, providing **7k** and **7l** with a quaternary carbon center, respectively. It is noteworthy that an acetoxy group at the allylic position of the dienophile alkene group can also be tolerated, giving **7m** with high diastereoselectivity (d.r. > 20:1) in 92% yield. This finding will be very important for diastereoselective total synthesis of natural product and potentially useful for the asymmetric synthesis through the chirality transfer of the substrates.

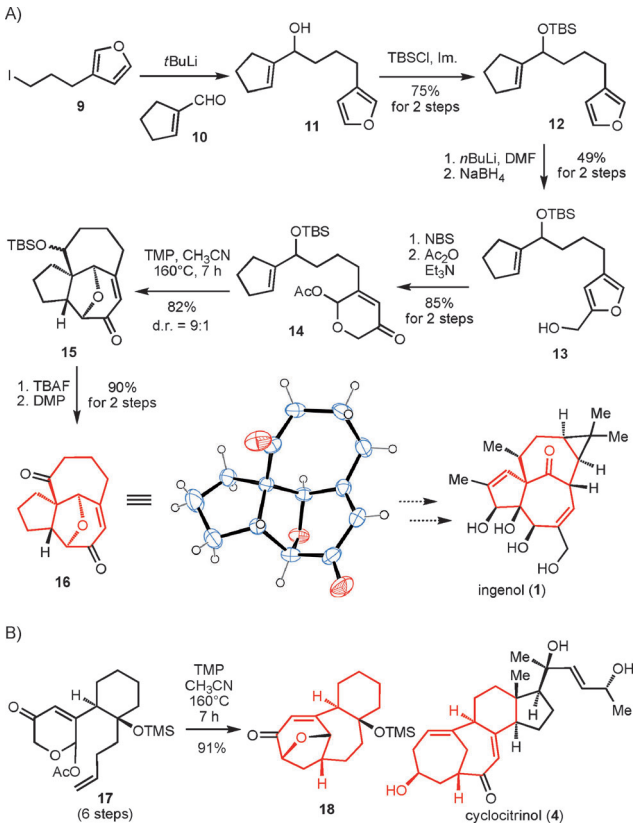
This methodology was then investigated for the generation of other bridged cycloheptane bicycles from substrates with tethers of various lengths (Scheme 3). Under similar conditions, bicyclo[4.3.1]decanes **7n** and **7o** and bicyclo[5.4.1]dodecane **7p** were formed. The more challenging bridged 7/9-bicycle bicyclo[6.4.1]tridecane **7q** was also obtained in good yield. Oxygen-tethered substrates were also tolerated, generating useful bridged cycloheptane bicycles (**7r–u**) in high yield. Upon treatment of **5t** with TMP at 100 °C, the terminal double bond migrated prior to the cycloaddition to give **7t** in 89% yield and with good diastereoselectivity (6:1 d.r.). Bicycle **7u** was isolated as the sole product from **5u**, indicating that the allenic ester forms before the cycloaddition under basic conditions and with heat. This product is difficult to access using other strategies. Additionally, after deprotection–oxidation, compounds **8a**, **8f**, **8j–l**, and **8p** were formed as single diastereomers (see the Supporting Information). The structure of one separable diastereoisomer of **7n**, with exclusive *endo* selectivity, was determined unambiguously using X-ray crystallography (Scheme 3B). These results showed that the type II intramolecular [5+2] cycloaddition reactions in Schemes 2 and 3 proceeded with exclusive *endo* selectivity.




***Scheme 3.*** Substrate scope using substrates with tethers of various lengths. [a] For X-ray structure, see bottom of the graphic.

In the total synthesis of natural products, it is particularly important that optically active molecules can be readily and reliably generated for the investigation of their biological activities. With this in mind, we evaluated the ability of optically active **5v** to undergo a stereospecific [5+2] reaction without effecting the existing stereochemisty. Under the optimized conditions (Scheme 3B), bicycle (+)-**7v** with a bridgehead all-carbon quaternary center was obtained with high diastereoselectivity (d.r. > 20:1) in 89% yield and 92% *ee* (see the Supporting Information). These results indicate that this [5+2] cycloaddition reaction is stereospecific, and that the chirality of the substrates effectively transfers to the products.

To demonstrate such a concept, the methodology was then applied to the highly strained tricyclic cores of ingenol and cyclocitrinol (Scheme 4). Readily available iodide **9** was converted to the corresponding alkyl lithium species and reacted with cyclopent-1-enecarbaldehyde **10** to give **11**. TBS protection of the resultant alcohol then gave **12**. Formylation of the furan in **12** and reduction of the aldehyde afforded




***Scheme 4.*** Synthesis of the cores of ingenol and cyclocitrinol.

alcohol **13** in an overall yield of 49%. Oxidative rearrangement of **13** using NBS and acetylation of the anomeric hydroxy group afforded acetoxypyranone **14** in 85% yield. Treatment of acetoxypyranone **14** under the optimized reaction conditions gave **15** in 82% yield and with high diastereoselectivity (9:1 d.r.). Subsequent TBS deprotection and oxidation afforded **16** as the sole product in 90% overall yield. The tricyclic core structure of **16** was unambiguously confirmed using X-ray crystallography, showing that the cycloaddition proceeded with exclusive *endo* selectivity. Using the similar route, acetoxypyranone **17** was prepared (see the Supporting Information). With the optimized reaction conditions, the tricyclic core **18** of cyclocitrinol (**4**) with a bridgehead double bond was obtained as the sole product in 91% yield. Total synthesis of these natural products using this strategy is ongoing.

In summary, here we have developed and reported the first type II intramolecular [5+2] cycloaddition reaction involving an oxidopyrylium ylide and a simple alkene, establishing a general protocol for the efficient and straightforward synthesis of many highly functionalized and challenging bridged cycloheptane bicyclic skeletons (such as bicyclo[4.4.1]undecane, bicyclo[4.3.1]decane, bicyclo[5.4.1]-dodecane, and bicyclo[6.4.1]]tridecane). The simple, thermal cycloadditions proceeded in high yield with unique *endo* selectivity[20] and had a broad substrate scope. The cyclization does not rely on the Thorpe–Ingold effect, which is a significant advantage over transition-metal-catalyzed cycloaddition. Furthermore, the enantioselective and diastereoselective formation of quaternary stereocenters, which are challenging to form using type II IMDA reactions,[12a] can also be achieved by using chiral starting materials. The described method enables the efficient single-step synthesis of the highly strained tricyclic cores of ingenol and cyclocitrinol. We believe that the reaction developed here may offer inspiration for the design of new strategies to prepare complex natural products and other bioactive molecules.

Received: November 6, 2014
Published online: December 10, 2014

**Keywords:** bridged ring systems · cycloaddition · diastereoselectivity · *endo* selectivity · natural products

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