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Dihydro- and tetrahydrofuran ring-opening reactions directed towards the synthesis of CP-263,114

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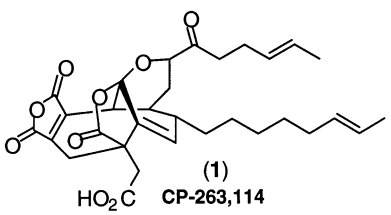
Abstract

An intramolecular 3+4 cycloaddition between vinylcarbenoids and furans followed by tetrahydrofuran ring-opening represents a direct approach for construction of the core of CP-263,114. © 2000 Published by Elsevier Science Ltd.

Recently, CP-263,114 (**1**) has become a synthetic target of great interest on account of its novel structure and promising biological activity.[1] The research activity in this area has included numerous model studies[2] and four recent reports of total syntheses of CP-263,114 by Nicolaou,[3] Danishefsky,[4] Shair[5] and Fukuyama.[6]



(1) CP-263,114

Intrigued by the possibility that an intramolecular [3+4] cycloaddition between vinylcarbenoids and furans would be a novel disconnection for the synthesis of CP-263,114, we have begun exploring the synthetic potential of this chemistry.[7] We have previously reported that the vinylcarbenoid precursor **2** available in three steps from methyl 4-formylfuran-3-carboxylate readily undergoes the 3+4 cycloaddition followed by bromination to form **3**.[7b] In this paper we describe our exploratory studies to develop methods for the conversion of the bromo derivative **3** to the bicyclo[4.3.1]nonane system **4**. The formation of **4** was considered to be an important stage for the eventual synthesis of CP-263,114 because **4** contains the anti-Bredt double bond, the hydroxy functionality at C-10, an α,β-unsaturated ester which Nicolaou used to generate the anhydride,[3] and the keto functionality at C-2 that Danishefsky used to generate the quaternary center at C-2 (Scheme 1).[4]

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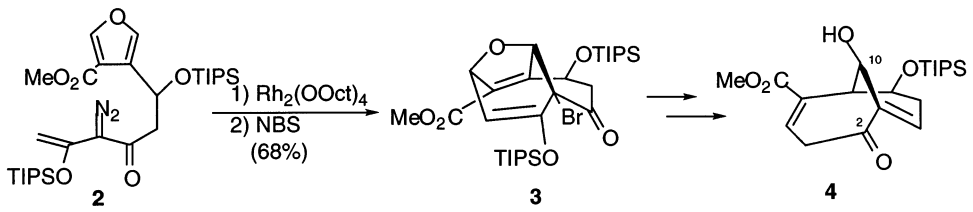
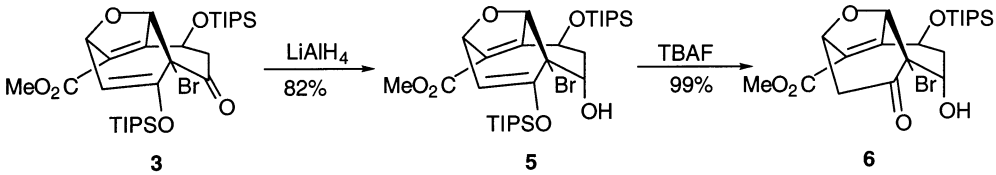


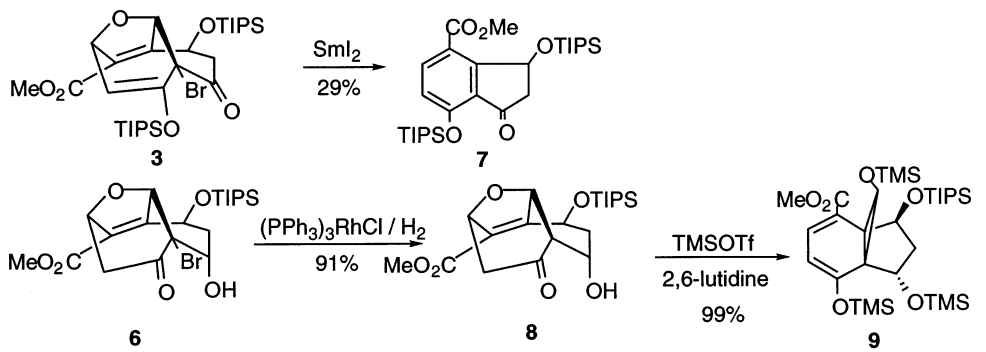
Scheme 1.

The previous synthetic endeavors directed towards CP-263,114 have shown that densely functionalized bicyclo[4.3.1]nonane systems display some unexpected reactivity.[3,4] Our initial studies also resulted in some unexpected reactivity. All attempts at catalytic hydrogenation of **3** were unsuccessful. Attempts at a retroaldol on **5** (readily formed from **3** by $LiAlH_4$ reduction[7b]) resulted in only desilylation to form **6**. Efforts to ring-open the dihydrofuran in **6** using a variety of bases or TMSOTf also failed (Scheme 2).



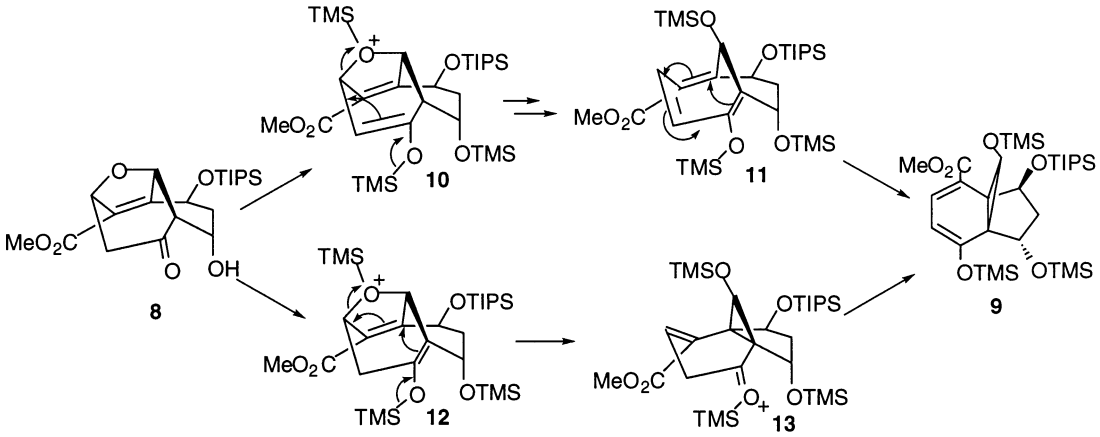
Scheme 2.

At this stage, it was considered that the bridgehead bromine functionality, which had been introduced to stabilize the initial [3+4] cycloadduct was now sterically interfering with the desired synthetic transformations. An attempt at removal of the bromide in **3** with samarium diiodide resulted in a major skeletal rearrangement and the dihydroindanone **7** was isolated in 29% yield. The clean removal of the bromine functionality was finally achieved by hydrogenation of **6** with Wilkinson's catalyst, which led to the formation of **8** in 91% yield. The de-brominated derivative **8** was still sluggish at ring-opening reactions of the dihydrofuran. Under forcing conditions, however, with an excess of TMSOTf, ring opening of the dihydrofuran in **8** was achieved, but the product was the unexpected norcaradiene derivative **9** (Scheme 3).



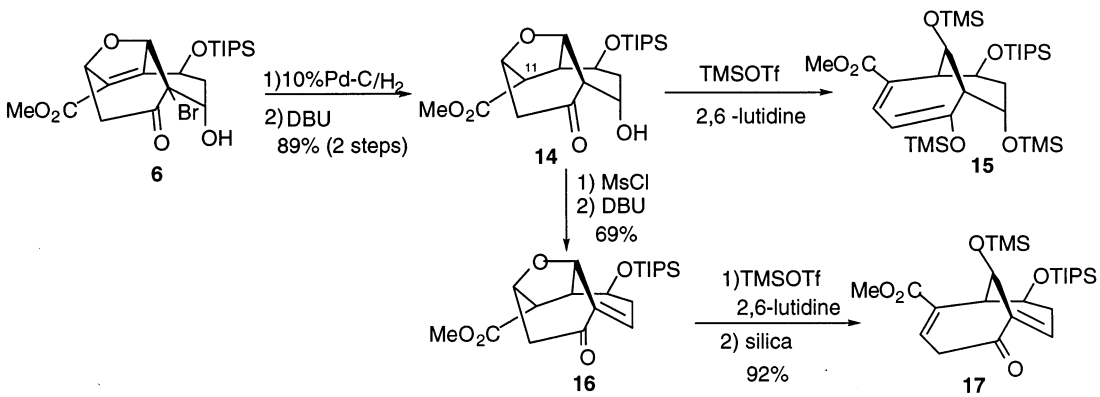
Scheme 3.

The unexpected formation of **9** is indicative of interference by the anti-Bredt double bond in **8** by one of two possible mechanisms. The silylated product **10** undergoes ring opening and deprotonation to form **11**, which is capable of a 6π electrocyclization to form **9**. Alternatively the silylated product **12** is initially formed and undergoes a transannular ring opening to form **13**, which after deprotonation forms **9**. Presumably, compound **3** is formed from an analogous compound to **9** through cyclopropane ring opening followed by aromatization by means of an oxidative deformylation (Scheme 4).



Scheme 4.

On the basis of the above analysis, it was concluded that it was necessary to remove the anti-Bredt double bond prior to the ring opening. Treatment of α,β-unsaturated ester **6** with 10% Pd–C under acidic conditions resulted in debromination as well as hydrogenation of the anti-Bredt double bond. A mixture of epimers at C-11 was initially formed but on treatment with DBU the mixture equilibrated to diastereomer **14**. Treatment of **14** with 5 equivalents of TMSOTf and 8 equivalents of 2,6-lutidine resulted in formation of the desired ring opened product **15** in almost quantitative yield. Having now developed an appropriate method for ring opening, via the tetrahydrofuran, a final series of experiments was carried out to determine if the ring opening could be achieved with the desired anti-Bredt double bond in place. Reaction of **14** with MsCl followed by reaction with DBU resulted in the formation of the anti-Bredt product **16**. Treatment of **16** with TMSOTf followed by silica gel resulted in a very clean ring opening to form **17** in 92% yield. (Scheme 5)



Scheme 5.

In summary, these studies demonstrate that further manipulation of the 3+4 cycloadduct to an appropriately functionalized [4.3.1]bicyclic system is possible. Having now demonstrated that the basic chemistry is applicable to the synthesis of the basic core of CP-263,114, future studies will be directed towards the application of the 3+4 cycloaddition to more highly functionalized systems so that a much shorter synthetic scheme can be developed.

Acknowledgements

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