



Cyclopropane ring-opening of tricyclo[3.3.0.0^{2,8}]octan-3-ones: a quick access to bicyclo[3.2.1]octanones from 2-methoxyphenols

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ABSTRACT

We herein report an efficient and rapid strategy for the synthesis of highly functionalized bicyclo[3.2.1]octanones via sequential reactions: Diels–Alder reaction of MOB–ODPM rearrangement–reductive cleavage of cyclopropane, and its application to synthesize the core structure of drechslerine D. © 2009 Elsevier Ltd. All rights reserved.

Bicyclic structures have been one of the main spotlights in synthetic chemistry over the years owing to their presence in a large number of natural products and synthetic challenges.¹ Among the derivatives of bicyclo[3.2.1] skeleton, drechslerine,² a small and rare family of sesquiterpenoids (Fig. 1), has drawn our attention with its structural uniqueness. Although there have been quite a few synthetic approaches developed over the years for the construction of bicyclo[3.2.1] skeletons through diverse chemical methodologies,³ synthesis of the drechslerine family natural products is yet to be reported. The installations of the fused lactone ring and the quaternary bridgehead on this bicyclic structure post a great challenge for synthetic chemists.

In the past, we have successfully demonstrated the power and potential of the chemistry of masked *o*-benzoquinones (MOBs) in organic syntheses to construct highly functionalized bicyclo[2.2.2]octenones,⁴ *cis*-decalins,⁵ bicyclo[4.2.2]- and bicyclo[3.2.2]-skeletons,⁶ linear and angular triquinanes⁷ skeletons from the Diels–Alder adducts of MOBs, and applied these synthetic strategies to the syntheses of natural products with diverse structural nature.⁸ The strategy that we have employed for the syntheses of triquinane/diquinane cores of capnellene,^{8d} magellanine,⁹ and forsythide aglucone dimethyl ester¹⁰ is the oxa-di- π -methane (ODPM) rearrangements of bicyclo[2.2.2]octenones, adducts from the Diels–Alder reactions of MOBs, followed by the reductive cleavage of the tricyclo[3.3.0.0^{2,8}]octan-3-ones (Scheme 1). As the cleavage of ‘a-bond’ yielded the diquinane skeleton, we foresee the cleavage of ‘b-bond’ of the ODPM rearrangement products would give an access to the corresponding bicyclo[3.2.1] skeletons. Though it has been reported that the cleavage of the cyclopropane ring in this tricyclic system typically took place at ‘a-bond’,^{7,11} examples of using nucleophilic addition¹² or functional group directing reductive cleavage¹³ to generate bicyclo[3.2.1]octanones from compounds of tricyclo[3.3.0.0^{2,8}] skeleton have also been reported. Thus as the

continuation of our efforts to develop new and efficient methodologies for the syntheses of natural products starting from 2-methoxy-

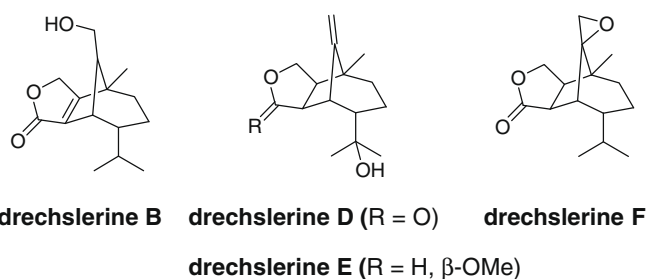
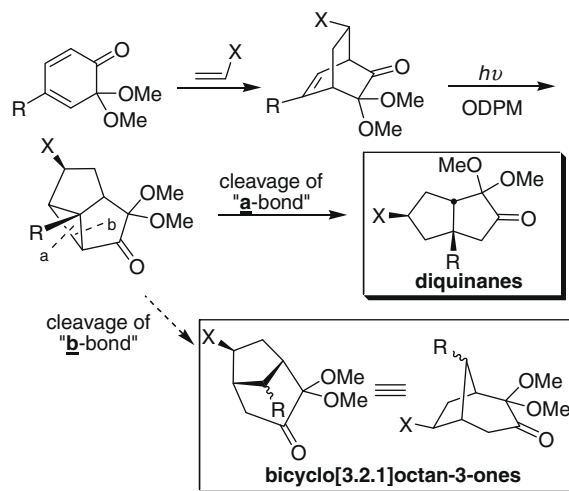


Figure 1. The drechslerine family natural products.



Scheme 1. Approach to diquinanes and bicyclo[3.2.1]octan-3-ones starting from MOBs.

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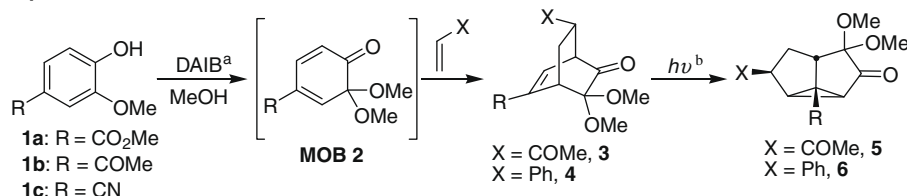
phenols via the corresponding MOBs, we report herein our results of the constructions of bicyclo[3.2.1]octanones from 2-methoxyphenols via sequential reactions: *Diels–Alder reaction of MOB–ODPM rearrangement–reductive cleavage of cyclopropane*.

In order to induce the desire selectivity of cleaving 'b-bond' over 'a-bond' in the forthcoming reductions of tricyclo[3.3.0.0^{2,8}]octan-3-ones obtained from the photoreaction,¹³ we deliberated to utilize MOBs with electron-withdrawing groups (R = CO₂Me, COMe, or CN), thus making the b-bond, connecting to the keto group of cyclopentanone and the R-substituent on the cyclopropane ring to be especially electron deficient and prone for the reduction to take place. The installation of the electron-withdrawing R-groups could also avoid the possibility of unwanted decarbonylation or other types of rearrangements during the triplet sensitized photoreactions.¹⁴ The results of the Diels–Alder reactions of selected MOBs^{8c,8d} and the following irradiation with 300 nm UV light in acetone with acetophenone as the sensitizer in a Rayonet reactor to give the ODPM rearrangement products are shown in Table 1.

The cycloadditions of MOBs and the subsequent photorearrangements gave moderate to excellent yields to the tricy-

clo[3.3.0.0^{2,8}]octan-3-ones, precursors for the next stage cyclopropane ring-opening reaction. The detailed experimental procedures and structural determinations with spectral data assignment are available in the [Supplementary data](#). After having compounds **5** and **6** in hand, we tried a number of reducing conditions. Messy mixtures were obtained from reactions using Li/NH₃¹⁵ and SmI₂^{7a,16} as reducing agents. Treatments of **5** and **6** with Zn/AcOH were found unreactive.¹⁷ However, reduction using *n*-Bu₃SnH, reported by Enholm,^{13a,13b} Lahiri,^{13c} and us,^{7b,9} was found to give the ring-opening reaction in clean and good yields (Table 2). The reductive cleavage reactions were directed by the adjacent carbonyl and electron-withdrawing R-groups and found to be completely chemoselective for the cleavage of 'b-bond'. The desired bicyclo[3.2.1]octanones were obtained in moderate to good yields. As we examined closely the stereochemistry of the reduced products, an inversion of configuration at the carbon center of the cyclopropane where the R-group is attached was found during the bond-breaking process (Fig. 2). This stereo-chemical outcome is presumably due to steric effect. In which during the cyclopropane ring-opening reaction, the late stage hydrogen abstraction of inter-

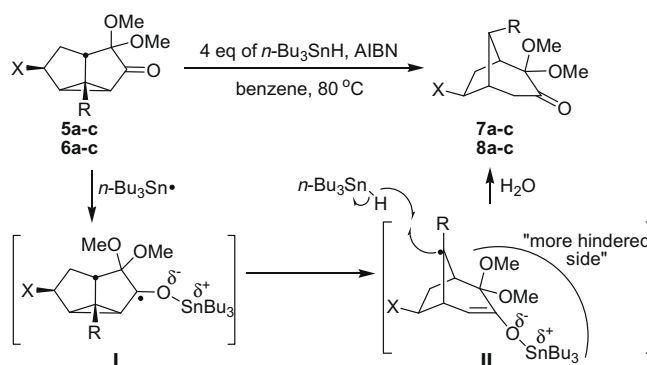
Table 1
Construction of tricyclo[3.3.0.0^{2,8}]octan-3-ones from MOBs



Entry	MOB	X	D–A adduct (%)	ODPM product (%)
1	2a	COMe	3a /87	5a /83
2	2b	COMe	3b /85	5b /93
3	2c	COMe	3c /44	5c /86
4	2a	Ph	4a /95	6a /90
5	2b	Ph	4b /93	6b /95
6	2c	Ph	4c /90	6c /96

^aDiacetoxyiodobenzene. ^bPhotolysis condition: *hν* = 300 nm, 10 equiv acetophenone, substrate as 1% solution in acetone.

Table 2
Reductive cleavage to yield bicyclo[3.2.1]octanones



Entry	R	X	Product (%)
1 (5a)	CO ₂ Me	COMe	7a /59
2 (5b)	COMe	COMe	7b /64
3 (5c)	CN	COMe	7c /51
4 (6a)	CO ₂ Me	Ph	8a /65
5 (6b)	COMe	Ph	8b /83
6 (6c)	CN	Ph	8c /40

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