Oxidative Dearomatization of *o*-Hydroxymethylphenol and Intramolecular $\pi^4s+\pi^2s$ Cycloaddition: An Expedient Synthesis of a Tricyclic Intermediate for Platencin

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Abstract: A synthesis of a tricyclic intermediate for platencin from a simple aromatic precursor is described. Oxidative dearomatization and intramolecular Diels–Alder reaction are key features of the approach.

Key words: oxidative dearomatization, intramolecular Diels–Alder reaction, cycloaddition, spiroepoxycyclohexa-2,4-dienone

Recently, novel terpenoids platencin (**1**)[1] and platensimycin (**2**,[2] Figure 1) were isolated by the Merck group.[1] Platensimycin and platencin have different carbocyclic frameworks containing the same side chain. Platensimycin (**2**) has a tetracyclic core structure containing a cyclic ether ring; whereas platencin (**1**) has a entirely different molecular structure containing a tricyclo[6.2.2.0^{1,6}]dodecane framework. Platencin acts as a dual inhibitor of FabH and FabF and exhibits a broad spectrum of antibacterial activity.[2] Platensimycin (**2**) is active against methycillin-resistant *S. aureus* (MRSA) and acts by blocking the enzyme FabF.[1] There has been significant interest in the synthesis of platensimycin[3,4] and platencin[5,6] due to their complex molecular architecture and potent antibacterial properties. Several ingenious approaches to platencin were reported soon after the elegant total syntheses by the groups of Nicolaou[5a] and Rawal.[5b] The majority of the routes to platencin proceed through tricyclic intermediate **3** (Figure 1). Nicolaou and co-workers prepared this intermediate from tricyclic enone **5** containing a bridged bicyclo[2.2.2]octane framework annulated with a six-membered ring through one of the bridgeheads.[5d]

It appears that the generation of functionalized bridged bicyclo[2.2.2]octane systems annulated with a six-membered ring poses a considerable synthetic challenge, and various types of strategies have been employed for the synthesis of the tricyclic core of platencin. Radical-induced rearrangement of bicyclo[3.2.1]octanes, radical cyclization, Diels–Alder reaction, and Ni(0)-mediated coupling approaches have been employed for the generation of the bicyclo[2.2.2]octane ring system of platencin.[5] A metathesis reaction was employed by Mulzer's group to create the bridged system of platencin,[5c,f] and an intramolecular Diels–Alder reaction has been used by the Nicolaou[5d] and Banwell groups.[5e]

Efficient generation of molecular complexity is one of the important aspects of designing synthesis,[7] and oxidative dearomatization of phenols has proved to be an important tool in this regard.[8,9] In continuation of our interest in generation molecular complexity from simple aromatics,[9] we recently reported[6b] a synthesis of dienone **3** employing tricyclic compound **4** that required deoxygenation of a car-

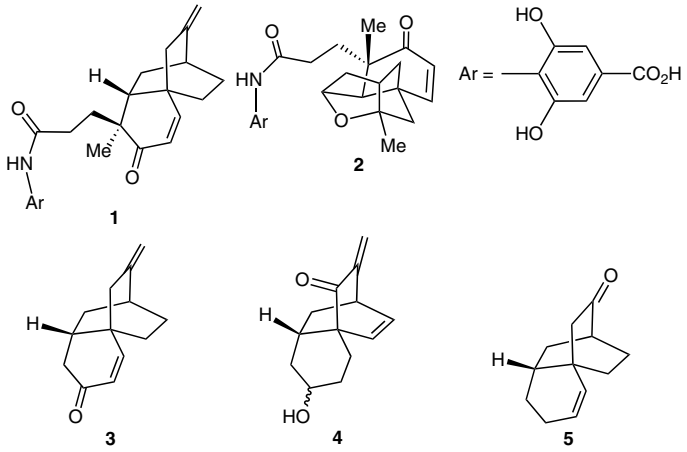

Figure 1 Platencin, platensimycin and intermediates

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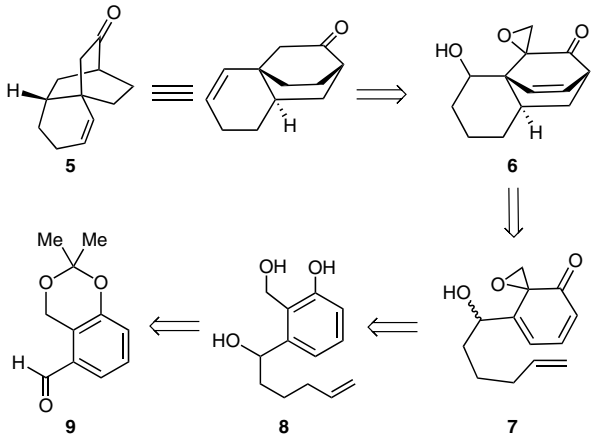
bonyl group. Hence, we considered devising a synthesis of the tricyclic intermediate **5** having an appropriately positioned carbonyl group that has been elaborated into platencin by Nicolaou and co-workers[5d] and wish to report our results herein.

Our strategy for the synthesis of tricyclic compound **5** is delineated in Scheme 1. It was contemplated that tricyclic intermediate **5** would be readily derived from keto epoxide **6** by manipulation of the oxirane ring, reduction of the double bond, and elimination of the hydroxyl group. The keto epoxide **6** was considered accessible from aromatic precursor **8** via oxidative dearomatization to form spiroepoxycyclohexa-2,4-dienone **7** followed by intramolecular Diels–Alder reaction. The aromatic precursor **8** was proposed to be accessible from the readily available aldehyde **9**.



Scheme 1

Some salient features of the above strategy are as follows. The tricyclic structure of the intermediate **5** is generated in a single step via stereoselective cycloaddition of embellished spiroepoxycyclohexa-2,4-dienone **7**. Furthermore, it is interesting to note that the aromatic precursor **8** contains all the carbon atoms of the intermediate **5** and its tricyclic ring system.

Conceptually, tricyclic compound of type **5** may also be obtained by intramolecular Diels–Alder reaction using cyclohexadienones such as **I** (Figure 2). However, the cyclohexa-2,4-dienone **I** is inaccessible as it is the keto tautomer of the corresponding phenol. Hence, the spiroepoxycyclohexa-2,4-dienone **7** was employed as an equivalent of **I** in order to realize our strategy.

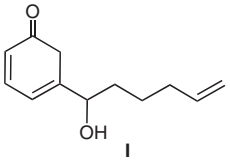
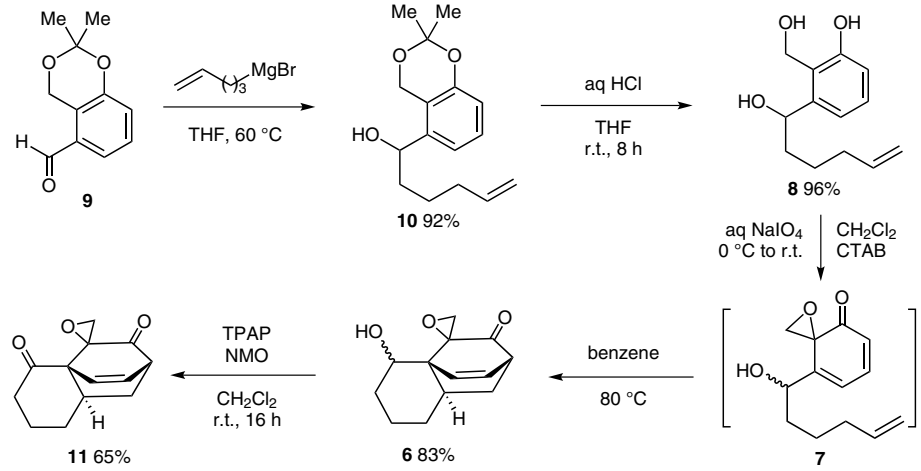


Figure 2 Theoretical Diels–Alder substrate

Thus, towards our objective, the aldehyde **9** was readily prepared[10] from 2,3-dimethyl phenol and converted into the aromatic precursor **8** and tricyclic adduct **6** as shown in Scheme 2. Treatment of aldehyde **9** with pentenyl magnesium bromide gave the alcohol **10** in excellent yield. Removal of the protecting group by aqueous HCl in THF readily furnished the aromatic precursor **8**. To achieve oxidative dearomatization and intramolecular cycloaddition, a solution of compound **8** in dichloromethane containing cetyltrimethylammonium bromide as a phase-transfer catalyst was oxidized with aqueous $NaIO_4$ following a method developed previously[11] in our laboratory. However, no cycloadduct was obtained; instead the cyclohexadienone **7** was formed. In contrast to the general tendency of spiroepoxy-cyclohexa-2,4-dienone towards dimerization, cyclohexadienone **7** was reluctant to undergo dimerization and yet it had only limited stability.

Therefore, the crude product obtained after oxidation of **8** was immediately dissolved in benzene and heated at 80 °C. Removal of solvent followed by chromatography gave the desired adduct **6** as a result of intramolecular cycloaddition in excellent yield as an inseparable mixture of diastereoisomers. The adduct **6** was then oxidized with TPAP–NMO to give the diketo epoxide **11** (Scheme 2). In principle, four stereoisomers of **6** could be formed during



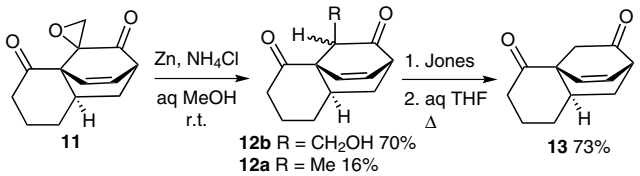
Scheme 2

the cycloaddition. However, it appears that only two are formed because spiroepoxycyclohexadienones are known to undergo highly stereoselective cycloaddition with regard to the orientation of oxirane ring wherein the oxirane methylene group remains *syn* to the double bond in the ethano bridge.[6b,8f]

The structure of adduct **6** and the diketo epoxide **11** were deduced from spectroscopic data. Thus, the IR spectrum of **11** showed absorptions at 1731 and 1712 cm^{-1} due to carbonyl groups, and the ^{1}HNMR spectrum (400 MHz, $CDCl_3$) displayed characteristic signals for olefinic protons at δ = 6.45 (dd, *J* = 8.2, 6.3 Hz, 1 H) and 6.22 (d, *J* = 8.2 Hz, 1 H) ppm due to the β and γ proton, respectively, of the β,γ-enone moiety. The methylene protons of the oxirane ring also exhibited highly characteristic signals at δ = 3.99 (part on an AB system, J_{AB} = 7.1 Hz, 1 H) and 2.98 (part on an AB system, J_{AB} = 7.1 Hz, 1 H) ppm. In addition, signals were observed at δ = 3.34–3.25 (m, 1 H), 2.68–2.55 (m, 1 H), 2.49–2.33 (m, 3 H), 1.98–1.70 (m, 3 H), 1.45–1.30 (m, 2 H) ppm. The ^{13}CNMR (100 MHz, $CDCl_3$) spectrum of compound **11** exhibited resonances at δ = 208.6 and 205.4 ppm due to carbonyl groups and olefinic carbons at δ = 133.4 and 130.3 ppm. Signals for other methine and methylene carbons were observed at δ = 59.2, 54.3, 52.5, 47.1, 40.1, 38.1, 31.8, 31.0, 23.9 ppm (total 13 carbons). These features clearly supported the structure of diketo epoxide **11**.

The stereochemical orientation of the oxirane ring, though it would be lost during further transformation, was proposed on the basis of the general reactivity of cyclohexadienones in cycloadditions. The *endo* stereostructure of compound **6** and **11** was not obvious from spectroscopic data alone and hence it was confirmed through chemical transformation and crystal-structure determination of a derivative (vide infra).

Thus, the diketo epoxide **11** was reduced with Zn and NH_4Cl in aqueous methanol at ambient temperature to give hydroxymethyl dione **12b** as a major product and **12a** as a minor compound. Oxidation of **12b** with Jones reagent followed by decarboxylation furnished the dione **13** in good yield (Scheme 3) as a crystalline solid whose structure was confirmed through single-crystal X-ray analysis.[12]



Scheme 3

The ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **13** also displayed characteristic resonances at δ = 6.34 (superimposed dd, *J* = 8.0 Hz, 1 H), 6.20 (d, *J* = 8.0 Hz, 1 H), and 3.11–3.09 (m, 1 H) ppm due to the β-, γ-olefinic protons of the β,γ-enone, and bridgehead proton, respectively. The multiplet at δ = 3.11–3.09 (m, 1 H) ppm was assigned to the bridgehead proton as it showed a correlation with the signal at δ = 6.34 ppm in the COSY spectrum. Other signals were observed at δ = 2.55 (td, J_1 = 13.8 Hz, J_2 = 6.1 Hz, 1 H), 2.44–2.31 (m partly overlapped with part of an AB system, *J* = 18.9 Hz, total 2 H), 2.17 (ddd, J_1 = 13.0 Hz, J_2 = 9.4 Hz, J_3 = 2.5 Hz, 1 H), 2.05–1.95 (m, merged with a part of an AB system, J_{AB} = 18.9 Hz, total 3 H), 1.72–1.58 (m, 2 H), 1.32 (d of an AB system, J_1 = 13.0 Hz, J_2 = 3.5 Hz, 1 H), and 1.18 (m of d, *J* = 13.0 Hz, 1 H) ppm due to other methine and methylene protons. The ^{13}C NMR spectrum (100 MHz, $CDCl_3$) exhibited characteristic signals at δ = 210.7, 210.6, and 134.5, 129.5 ppm due to carbonyl and olefinic carbons, respectively. Other methine and methylene carbons showed resonances at δ = 54.9, 48.9, 43.4, 40.7, 38.9, 32.0, 30.5, 26.3 ppm (total 12 carbons). A single-crystal structure determination of compound **13** confirmed its stereostructure (Figure 3) and thus established the structure of its precursors.

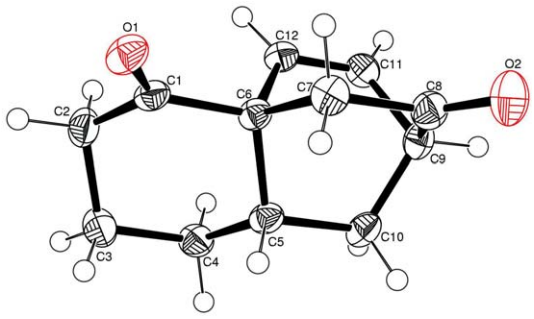
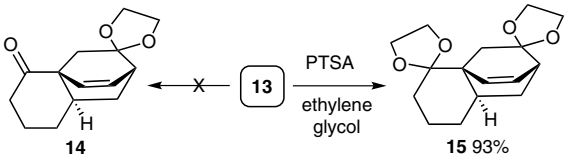


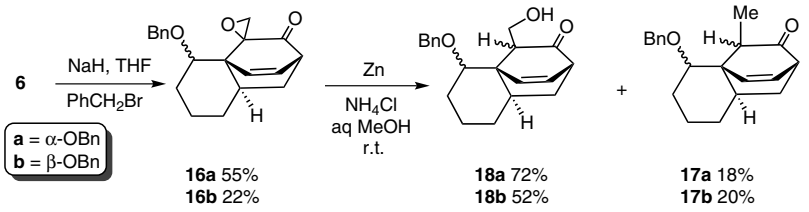
Figure 3 Crystal structure of compound **13**

In order to prepare the intermediate **5** from **13**, we considered selectively protecting the carbonyl group present on the ethano bridge in order to manipulate the other CO group and introduce the double bond into the cyclohexane ring. Unfortunately, treatment of dione **13** with ethylene glycol in the presence of *p*-toluenesulfonic acid did not give **14**; instead the bisketal **15** was obtained as a result of protection of both CO groups (Scheme 4).

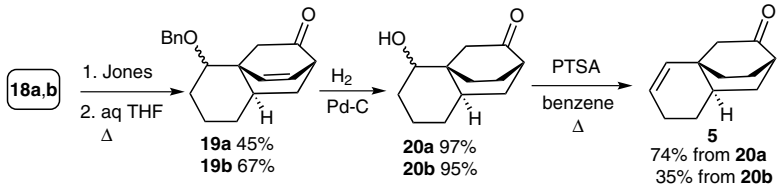


Scheme 4

Therefore, we developed an alternate route to tricyclic compound **5** from the adduct **6** as shown in Scheme 5. Thus, the adduct **6** was treated with NaH/THF and benzyl bromide which gave benzylated products **16a** (major) and **16b** (minor) that were separated by column chromatography. Based on the formation of benzylated products **16a**,**b** the ratio of the corresponding isomers in **6** appears to be 2.5:1. The stereochemical orientation of the benzyl group



Scheme 5



Scheme 6

in **16a**,**b**, though inconsequential, was suggested on the basis of chemical shift, multiplicity, and coupling constant of the proton attached to the carbon bearing an OBn group (*H*COBn). Thus, the ^{1}HNMR spectrum of the major isomer **16a** exhibited a characteristic signal at δ = 3.76 ppm as a broad doublet (J = 1.6 Hz) due to the *H*COBn proton that clearly suggested the orientation of the proton as equatorial. On the other hand, the *H*COBn proton in the minor isomer **16b** appeared at higher field δ = 3.15 ppm as a doublet of doublets (J_1 = 11.0 Hz, J_2 = 4.7 Hz); the large coupling constant (J_1) being due to the diaxial coupling with the axial proton of the adjacent methylene, with J_2 being due to the coupling with the equatorial proton. These features clearly suggested the orientation of the OBn groups. This trend in the chemical shift and coupling constant was also observed in other derivatives. Reduction of **16a** and **16b** with Zn and NH_4Cl in aqueous methanol at ambient temperature gave the β-hydroxymethyl ketones **18a** and **18b**, respectively, as major products and **17a**,**b** as minor compounds (Scheme 5).

Oxidation of **18a**,**b** with Jones reagent followed by decarboxylation furnished **19a**,**b** that upon treatment with H_2/Pd/C gave the keto alcohols **20a**,**b** in excellent yield. Here also the chemical shift and coupling constant of the *H*COH proton clearly revealed the stereochemical orientation of the hydroxyl group. Towards the synthesis of intermediate **5**, a solution of keto alcohol **20a** in benzene containing *p*-toluenesulfonic acid was heated to reflux to give the desired compound **5** in very good yield (Scheme 6). The dehydration of the other isomer **20b**, however, was sluggish and gave the product in moderate yield along with the unreacted starting material. The relative reactivity of **20a** and **20b** is a manifestation of the stereochemical orientation of the hydroxyl groups and the stereoelectronics involved during the elimination. The hydroxyl group in **20b** is present in equatorial position and hence does not undergo efficient elimination.

The structure of the enone **5** was deduced from its spectroscopic features which are in agreement with those reported by Nicolaou and co-workers.[5d] The enone **5** has already been elaborated into platencin,[5d] thus this approach constitutes a formal total synthesis.

In summary, we have developed a route to tricyclic intermediate for the synthesis of platencin from a simple aromatic precursor. Our methodology involves oxidative dearomatization and intramolecular Diels–Alder cycloaddition as key steps. The present synthesis demonstrates the synthetic potential of the oxidative dearomatization of *o*-hydroxymethylphenols and spiroepoxycyclohexa-2,4-dienones and constitutes a good example of efficient creation of structural, functional, and stereochemical complexity from simple aromatic precursors.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **Crystal Data for 13**
$C_{12}H_{14}O_2$, M = 190.23, monoclinic, space group $P2_1/n$, a = 6.4692(3) Å, b = 21.7808(6) Å, c = 7.3963(3) Å, α = 90°, β = 113.217(4)°, γ = 90°, V = 957.77(6) Å^3, D_c = 1.319 Mg m^{-3}, Z = 4, $F(000)$ = 408, size: 0.33 × 0.26 × 0.21 mm^3, wavelength = 0.71073 Å, GoF = 1.077, absorption coefficient = 0.088 mm^{-1}, total/unique reflections = 6555/1684 [R_{int} = 0.0138], T = 150(2) K, θ range = 3.53–24.99°, final R [$I > 2\sigma(I)$]: $R1$ = 0.0317, $wR2$ = 0.0791, R (all data): $R1$ = 0.0366, $wR2$ = 0.0808. Crystallographic data has been deposited with Cambridge Crystallographic data Centre, CCDC no. 925908. Copy of the data can be obtained, free of charge, on application to CCDC. E-mail. deposit@ccdc.cam.ac.uk.

