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Dichlorocarbene adducts of alkyl enol ethers as precursors to furans: application to a total synthesis of the furanosesquiterpene (±)-pallescensin A

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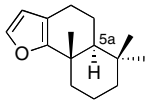
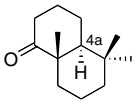
Abstract—A novel method for annulating furans to ketones, involving treatment of the dichlorocarbene adduct of the derived methyl enol ether with base, has been exploited in the synthesis of the title natural product **1** from the known *trans*-decalone **2**.

The furanosesquiterpenes constitute a very large and ever-growing class of natural products that have been derived from both terrestrial and marine organisms.[1] The first members of the class were isolated more than 80 years ago but their structures were not firmly established until the early 1950s.[2] Over the intervening years, the associated furan ring has been found linked with or fused to a wide range of terpenoid frameworks including the farnesane, bisabolane, cadinane, germacrane, eudesmane, elemane, lindenane, and eremophilane skeleta.[2,3] A variety of modest biological activities have been observed for many furanosesquiterpenes but the presence of the furan ring does not engender any specific properties. Nevertheless, such terpenoids have attracted the attention of organic chemists and a range of useful methods for their preparation have emerged.[3] A number of these have provided new protocols for annulation of the furan ring to carbocyclic frameworks.[3] Herein, therefore, we wish to highlight a complementary approach that allows for the three-step conversion of an enolizable cyclic ketone into the corresponding furannulated system. This conversion involves, as the key step, treatment of the dichlorocarbene adduct of the alkyl enol ether derivative of the starting carbonyl with base[4] and we have exploited it for the preparation of the racemic modification of the furanosesquiterpene pallescensin A (**1**) from decalone **2**.[5]

Pallescensin A was first obtained from the marine sponge *Disidea pallescens*[6] and it is likely to be biogenetically derived from a furanoid mono-cyclofarnesane precursor. It has been suggested that the compound is involved in the defensive mechanisms employed by opisthobranch molluscs, which concentrate such sponge metabolites in their skin and then release them when they come under attack.[3] The absolute configuration of compound **1** was established by total synthesis from (*R*)-(−)-α-cyclocitral and via a reaction sequence involving a biomimetic cyclization process.[7] Since then some nine additional syntheses of pallescensin A have been reported[8] including three[8c,e,g] that involve compound **2** as a precursor. These require ten, five or three steps to achieve the required furannulation process and so complete the synthesis of target **1**.



1



2

Several different routes have been used to prepare decalone **2**[9] although all these begin with the Wieland–Miescher ketone (**3**).[10] We chose to follow the protocols recently described by Katerinopoulos et al.[9b] but some

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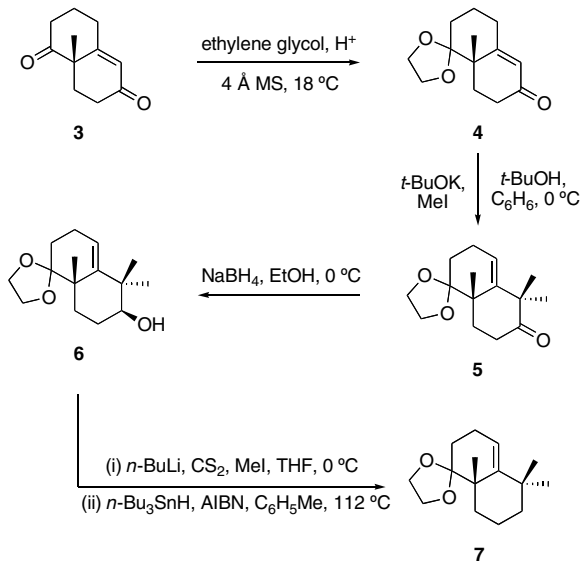
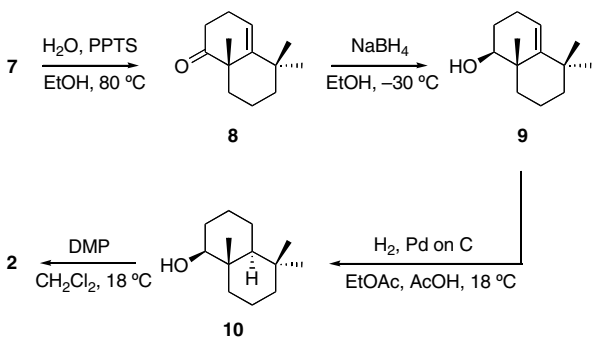


Scheme 1.

modifications, as detailed below, were required. In the early stages of the reaction sequence (Scheme 1), the racemic modification of ketone **3** was selectively converted into ethylene ketal **4** (70%) and this was then treated with a mixture of potassium *tert*-butoxide, *tert*-butanol, and methyl iodide according to a method originally defined by Woodward and Barton,[11] then exploited for the present purpose by Demnitz.[12] Attempts to remove the carbonyl group within the product ketone **5** (77%) using the Huang–Minlon modification of the Wolff–Kischner reduction, as outlined by both Katerinopoulos[9b] and Quayle,[13] did not provide preparatively useful quantities of the desired product. As a result, a stepwise protocol for effecting this conversion was used and this exploited a Barton–McCombie reaction as applied by Hagiwara and Uda[14] to a closely related system. Thus, reduction of ketone **5** with sodium borohydride occurred stereoselectively to give β-alcohol **6**[15] in 95% yield. The xanthate ester derived from the latter compound was then treated, in refluxing toluene, with tri-*n*-butyltin hydride and AIBN to afford the target decalin **7** (82% from **6**).

The conversion of compound **7** into the ketone, **2**, required to test our furannulation protocol is shown in Scheme 2. So, hydrolysis of the ketal unit within the former material using aqueous ethanol as solvent and pyridinium *p*-toluenesulfonate (PPTS) as catalyst afforded compound **8** (89%) that was then reduced stereoselectively to the corresponding unsaturated alcohol **9** (99%) with sodium borohydride. The Pd on C-catalyzed hydrogenation of alkene **9** failed when hexane/ethanol mixtures were used as the reaction medium[9b] but this conversion was readily accomplished in ethyl acetate, provided it contained small amounts of acetic acid. Two chromatographically separable products of reaction were obtained, namely the expected alcohol **10** (46%) and the corresponding ketone **2** (39%), the structure of which was confirmed by single-crystal X-ray analysis (Fig. 1).[16] The second product is presumed to arise by a Pd-catalyzed migration of the double bond within precursor **9** and so leading to the formation of the enolic tautomer of compound **2** in the first instance. Oxidation of alcohol **10** using the Dess–Martin periodinane (DMP)[17] provided further quantities (82%) of ketone **2** that proved identical with the samples obtained from the hydrogenation reaction. The spectral data derived from these samples of compound **2** matched those reported previously,[9] but also revealed that this was contaminated with small quantities (ca. 5%) of its cis-isomer 4a-*epi*-**2**.



Scheme 2.

The three-step conversion of ketone **2** into (±)-pallescensin A (**1**) (Scheme 3) involved an initial reaction of the former compound with trimethyl orthoformate and methanol in the presence of catalytic quantities of *p*-toluenesulfonic acid. The resulting unstable red oil, containing mixtures of the expected methyl enol ether and the starting ketone, was subjected to reaction with dichlorocarbene generated under Makosza's phase-transfer conditions [$CHCl_3$, 50% aq NaOH, triethylbenzylammonium chloride (TEBAC)].[18] In this manner, the starting ketone **2** was obtained (27% recovery) along with a chromatographically inseparable and ca. 1:1 mixture of the dichlorocyclopropanes **11** and **12** (53% combined yield). This mixture also contained small quantities (ca. 5%) of a single diastereoisomeric form of cyclopropane **13** that is presumed to arise from carbene addition to the cis-ring fused isomer of compound

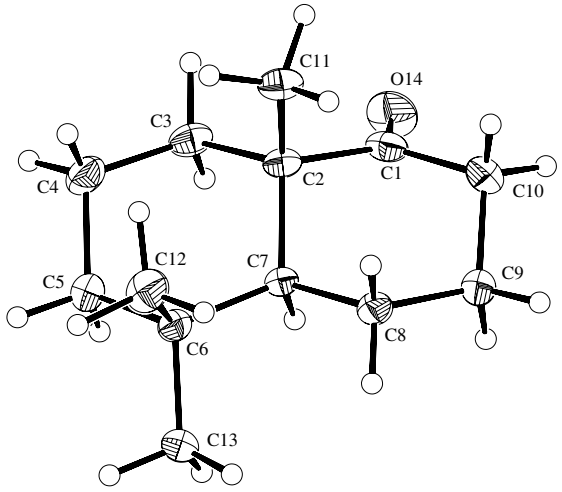
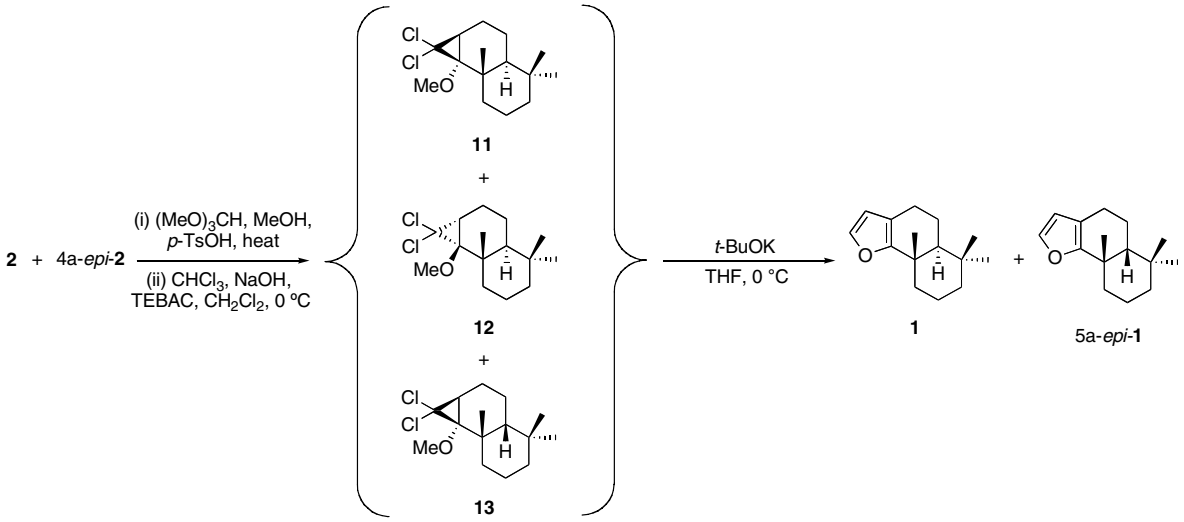


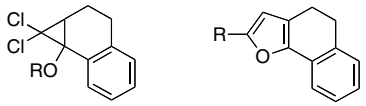
Figure 1. ORTEP derived from the single-crystal X-ray analysis of **2**.



Scheme 3.

2. Treatment of the mixture of cyclopropanes **11**–**13** with potassium *tert*-butoxide in THF at 0 °C for 2 h[19] afforded a chromatographically separable mixture of (±)-pallescensin A (**1**, 38%) and its cis-isomer (5%). The spectral data[19] derived from these furanoid products were very similar to one another and matched those reported in the literature.[7,8c] Since the Wieland–Miescher ketone (**3**) is available in enantiomerically pure form through the D- or L-proline-catalyzed Robinson annulation of 2-methylcyclohexa-1,3-dione with methyl vinyl ketone,[20] the chemistry detailed above should be applicable to the synthesis of either the (+)- or (−)-forms of pallescensin A.

The utility of the title process is further demonstrated by the observation that the readily available cyclopropanes **14**[21] and **15**[21,22] each react with potassium *tert*-butoxide in THF to give the annulated furans **16**[23] (72%) and **17**[24] (88%), respectively.



14 R=Me
15 R=Et

16 R=H
17 R=Me

The conversion of the above-mentioned *gem*-dichlorocyclopropanes into the corresponding furans may well proceed in the manner defined by Müller and Pautex.[4] Thus, initial based-induced elimination of the elements of HCl from within these substrates would generate the corresponding ring-fused cyclopropene that rearranges to the isomeric vinylcarbene. This last species then undergoes insertion into one of the α-C–H bonds of the adjacent methoxy or ethoxy group to afford a chlorodihydrofuran that loses a second equivalent of HCl and so generating the observed product.[25] Experimental and theoretical studies of this and other reaction pathways are now underway in our laboratories. The results will be reported in due course.

Acknowledgments

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19. Preparation of (±)-pallescensin A (**1**). A magnetically stirred solution of the mixture of cyclopropanes **11**–**13** (160 mg, 0.55 mmol) in THF (10 mL) maintained at 0 °C under a nitrogen atmosphere was treated with potassium *tert*-butoxide (370 mg, 3.3 mmol). After 2 h at this temperature TLC analysis revealed that all of the starting materials had been consumed. Consequently, water (5 mL) was added to the reaction mixture and the separated aqueous phase extracted with diethyl ether (2×10 mL). The combined organic phases were then washed with brine (1×5 mL) before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil (130 mg). Subjection of this material to flash chromatography (silica gel, *n*-hexane elution) afforded two fractions, A and B. Concentration of fraction A ($R_f = 0.3$) afforded (±)-pallescensin A (**1**) (46 mg, 38%) as a clear, colorless oil (Found $M^{+\cdot}$, 218.1678. $C_{15}H_{22}O$ requires $M^{+\cdot}$, 218.1671). ^{1}H NMR (800 MHz, $CDCl_3$) δ 0.91 (s, 3H), 0.94 (s, 3H), 1.20 (s, 3H), 1.24 (td, $J = 12.8$ and 4.0 Hz, 1H), 1.38 (m, 2H), 1.49 (dm, $J = 13.6$ Hz, 1H), 1.54–1.60 (complex m, 2H), 1.72 (qt, $J = 13.6$ and 3.2 Hz, 1H), 1.85 (dd, $J = 12.8$ and 6.4 Hz, 1H), 2.12 (dm, $J = 12.8$ Hz, 1H), 2.37 (m, 1H), 2.49 (dd, $J = 16.0$ and 6.4 Hz, 1H), 6.12 (d, $J = 1.8$ Hz, 1H), 7.19 (d, $J = 1.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 19.5, 21.3, 21.4, 22.7, 33.0, 33.4, 35.5, 36.5, 41.9, 52.3, 110.1, 113.7, 140.0, 159.8; ν_{max} (neat)/cm^{-1} 2929, 2866, 1503, 1457, 1375; *m*/*z* (EI) 218 ($M^{+\cdot}$, 85%), 203 (100). Concentration of fraction B ($R_f = 0.4$) afforded the cis-isomer of compound **1** (6 mg, 5%) as a clear, colorless oil.
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