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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 8717–8720

Investigations towards the synthesis of (−)-coprinolone, via a thermal 8π–6π electrocyclization cascade of 1,5,7-trien-4-ones

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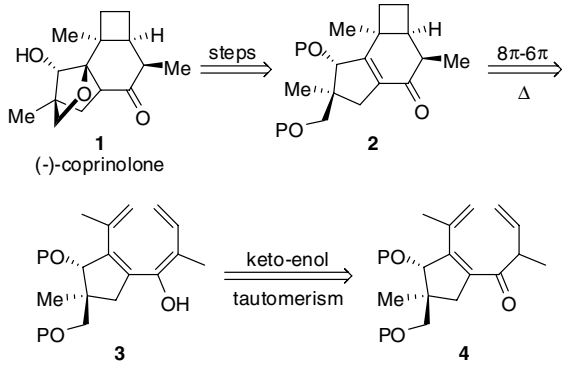
Received 9 August 2006; revised 26 September 2006; accepted 5 October 2006

Abstract—Herein the investigation of a thermal 8π–6π electrocyclization cascade of 1,5,7-trien-4-ones, as a key step towards the synthesis of (−)-coprinolone is described.

(−)-Coprinolone **1** is an unusual oxygen-bridged protoilludane sesquiterpene ketol, isolated from the fungus *Coprinus psychromorbidus*, which has been the subject of many studies due to the extensive damage it causes to overwintering cereals, grasses and legumes in western Canada.[1,2] The unusual tricyclic ether bridged structure of (−)-coprinolone **1** with its seven chiral centres, two of which are quaternary, makes it an attractive target for synthetic study. Pericyclic reactions have the capacity to fix the stereochemistry of contiguous chiral centres, and so an electrocyclic approach may well be an attractive way to form (−)-coprinolone **1**.

The thermal 8π–6π electrocyclic ring closure of 1,3,5,7-tetraenes has been utilized in the total synthesis of a number of natural products.[3] It is postulated that the tricyclic structure of (−)-coprinolone **1** could be constructed using a thermal 8π–6π electrocyclization of a trienone **4** (Scheme 1). To the best of our knowledge there has only been one reported example, by Snider et al., of the thermal 8π–6π electrocyclic ring closure of a trienone.[4] In Snider's example a 2,5,7-trien-4-one was postulated to first isomerize to an intermediate 1,5,7-trien-4-one which then cyclized to a bicyclo-[4.2.0]octenone in a combined yield of 29% for three different diastereomeric products.[4]

The electrocyclization of trienones was investigated on model systems, to determine whether a thermal 8π–6π electrocyclic ring closure of a preformed 1,5,7-trien-4-one may be a possible route to the cyclic sub-structure of (−)-coprinolone **1**. Four trienones **16**–**19** differing in their ketone α-substituents have been synthesized (Scheme 2) and their electrocyclic ring closure observed under heating in polar solvents (DMSO, MeOH) (Table 1).



Scheme 1. A proposed retrosynthetic analysis of (−)-coprinolone **1**.

The synthesis began with conversion of the commercially available β-keto ester **5** to vinyl triflate **6**,[5] which was then used in a Suzuki–Miyaura cross-coupling reaction with isopropenyl pinacolboronic ester **7**,[6] prepared from the isopropenyl Grignard reagent.[7] The resulting ester **8** was then treated with DIBAL-H[8] followed by MnO_2[9] to give the corresponding aldehyde **10**. Luche coupling was carried out with aldehyde **10** and the appropriate allylic bromides to give alcohols **12**–**15**.[10]

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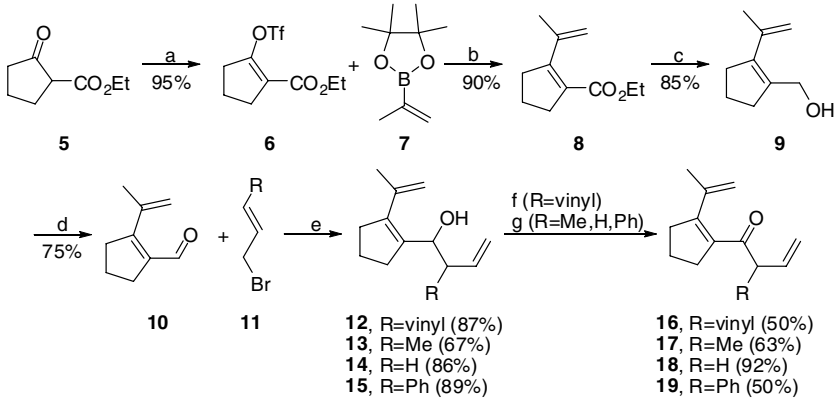
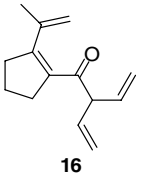
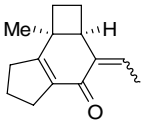
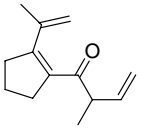
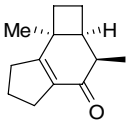
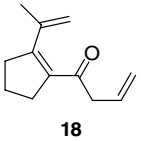
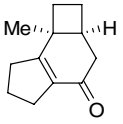
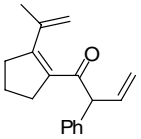
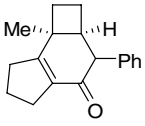
doi:10.1016/j.tetlet.2006.10.021



Scheme 2. Synthesis of 1,5,7-trien-4-ones **16**–**19** from β-keto ester **5**. Reagents and conditions: (a) Tf_2O, $^iPr_2NEt$, DCM, −78 °C; (b) (dppf)$PdCl_2$, K_3PO_4, DMF, 60 °C; (c) DIBAL-H, Et_2O, −78 °C; (d) MnO_2, DCM; (e) Zn, $NH_4Cl_{(aq)}$–THF (1:2), 0 °C; (f) DMP, DCM; (g) IBX, DMSO.

Table 1. Electrocyclization of 1,5,7-trien-4-ones **16**–**19**

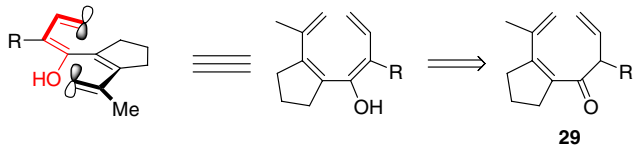
Entry	Trienone	Cyclized product	Conditions	Yield (%)
1			DBU (10 equiv), DMF, 120 °C [4]	0
2	 **16**	 **20**(*Z*), **21**(*E*)	(i) LDA, 0 °C, TMSCl, THF (ii) Benzene, Δ, sealed tube (iii) TBAF, 0 °C	31[a]
3			DMSO, 100 °C, 2 h	59[b]
4			DMSO, 150 °C, 1 h	9
5	**17**	**22**	MeOH, 110 °C, 24 h	33
6	 **18**	 **23**	MeOH, 110 °C, 3.5 h	24
7	 **19**	 **24**	MeOH, 120 °C, 11 h	<8[c]

[a] Exclusive formation of *E*-isomer **21**.
[b] Ratio of 11:1 for *Z*(**20**):*E*(**21**).
[c] Yield by mass of a mixture of cyclic product **24** and unidentifiable by-products.

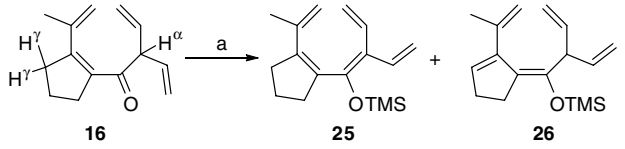
These alcohols were then oxidized to the corresponding ketones **16**–**19** using either IBX[11] or DMP.[12]

The thermal 8π–6π electrocyclization of trienone **16** was first investigated, as there are no issues regarding the *E*/*Z* geometry of the intermediate enolate with this system (Scheme 3). Initially the conditions used by Snider and Harvey[4] were tried but resulted in no cyclic products (Table 1, entry 1).

The formation of a TMS trapped enolate followed by heating in benzene and subsequent TBAF deprotection



Scheme 3. Required geometry of the enolic double bond for correct orbital overlap.



Scheme 4. Possible γ- versus α-deprotonation of 1,5,7-trien-4-one **16**. Reagents and conditions: (a) LDA, 0 °C, TMSCl, THF.

was carried out, resulting in a 31% yield of the cyclic product **21** with the double bond geometry determined by a NOESY experiment (Table 1, entry 2). ^{1}H NMR spectra of the crude TMS trapped enolate taken before and after heating in benzene showed that a minor olefinic species was formed which was converted to **21** upon heating. However, another major species was also present with olefinic protons which did not undergo the electrocyclization. We put forward the hypothesis that some competing γ-deprotonation may be taking place resulting in the formation of TMS enolate **26**, which cannot undergo the electrocyclic ring closure (Scheme 4).[13]

Mills and Beak reported in 1985 that the equilibrium constant for keto-enol tautomerism is dominated by the polarity and hydrogen bonding basicity of the solvent.[14] It was envisaged that in a polar and/or hydrogen bond acceptor solvent the enol form of trienone **16** may directly undergo the cyclization in situ. Therefore, trienone **16** was heated to 100 °C in DMSO and pleasingly cyclic ketones **20** and **21** were isolated in 54% and 5% yields, respectively (Table 1, entry 3). The exclusive formation of the *E*-isomer **21** via cyclization of the TMS trapped enolate (Table 1, entry 2) is in contrast to the preferential formation of *Z*-isomer **22** by a simple heating in DMSO (Table 1, entry 3). We suggest that this can be accounted for by kinetic formation of *Z*-isomer **20** by intramolecular keto-enol tautomerism of the cyclized intermediate **28** (Scheme 5). A crystal structure of *Z*-isomer **20** of the cyclic ketone was obtained (Fig. 1).[15]

With trienone **16** successfully cyclized in a 59% yield it was decided to attempt the cyclization of trienone **17**, which more closely resembles precursor **4**, as it has a methyl group α to the ketone. It was found that using

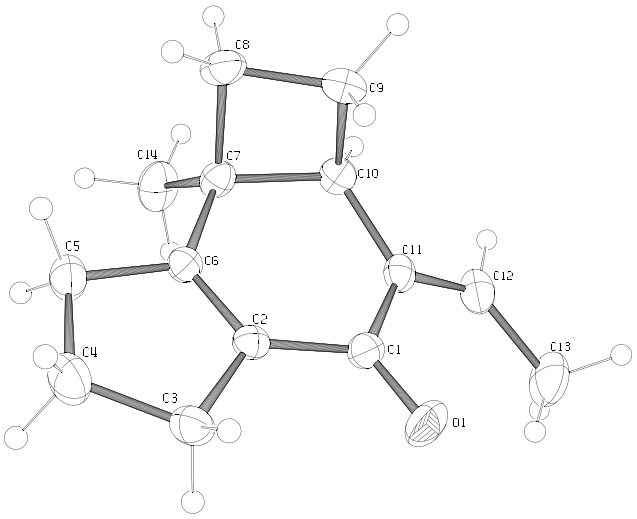
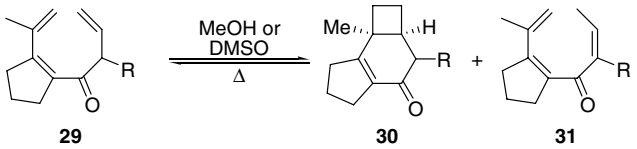


Figure 1. X-ray crystal structure of cyclic product **20**.[15]

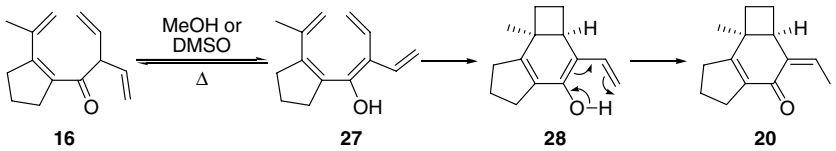
DMSO as the solvent resulted in a yield of 9% of the cyclized product **22**, which was shown to have the same relative stereochemistry as (−)-coprinolone **1** via NOE experiments (Table 1, entry 4). The conditions were further optimized for trienone **17**, with MeOH resulting in the best yield of 33% (Table 1, entry 5). Trienone **18** was also cyclized to product **23** in a 24% isolated yield (Table 1, entry 6).

A by-product in all the attempted cyclizations was the corresponding trienone **31**, where Δ-1,2 had moved to form Δ-2,3, which is in conjugation with the ketone (Scheme 6). The cyclization of trienone **17** was carried out in methanol-d_4, and carbon NMR showed that formation of the conjugated trienone **31** (R = Me) was irreversible, as no deuterium was incorporated in the cyclobutane ring of tricyclic ketone **22**.

To confirm that the formation of the conjugated trienone **31** was irreversible we decided to attempt the cyclization of α-phenyl trienone **19**. Trienone **19** was subjected to heating in MeOH and gave the cyclized ketone **24** recovered in a mixture with other unidentifiable products in a low yield of <8% by mass (Table 1, entry



Scheme 6. Thermal electrocyclization of a 1,5,7-trien-4-one **29** to form cyclic ketone **30**, and the conjugated by-product **31**.



Scheme 5. Isomerizations leading to preferential formation of *Z*-isomer **20**.

7), and conjugated ketone **31** (R = Ph) in a 24% yield. This is consistent with the facile permanent formation of conjugated trienone **31**, as a Ph substituent is more likely to isomerize to a favourable styrene moiety.

In conclusion, four 1,5,7-trien-4-ones **16**–**19**, with different substituents at the 3-position, have been synthesized (Scheme 2) and their 8π–6π thermal cyclization afforded, by simple heating in polar solvents (Table 1), products having key cyclic sub-structural features of (−)-coprinolone **1**. Application of this enolization–electrocyclization cascade reaction of 1,5,7-trien-4-ones towards the total synthesis of (−)-coprinolone **1** is under investigation.

Acknowledgements

We thank Dr. Andrew Cowley for X-ray crystal structure determination, Roche for funding to M.F.J. and the Ernst Schering Research Foundation for a Fellowship for H.A.W.

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15. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 611641. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].