



# Influence of ring fusion stereochemistry on the stereochemical outcome in photo-induced Diels–Alder reaction of fused bicycloheptenone derivatives



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## ABSTRACT

Photo-isomerization of *cis*-cycloheptenone fused to a ring with a defined stereochemistry at the ring fusion to its *trans*-stereoisomer and in situ Diels–Alder reaction with cyclic and acyclic dienes have been investigated. The reaction was found to proceed through one of the two possible isomerized *trans*-enones that produce the thermodynamically more stable adduct with a *trans*-fused seven-membered ring system. This protocol has been employed to construct a tetracycle with *trans*-fused 6–7 ring system, the core structure present in several terpenes. The observed selectivity has been supported by computational method.

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## 1. Introduction

A plethora of natural products of terpenoid origin is found to contain *trans*-fused 5/7 and 6/7 ring systems. The tricyclic diterpenes clavularane **1**,<sup>1</sup> cyanthiwigin U **2**,<sup>2</sup> and nor-triterpenoid lancifodilactone F **3**<sup>3</sup> (Fig. 1) are illustrative examples. A simple way

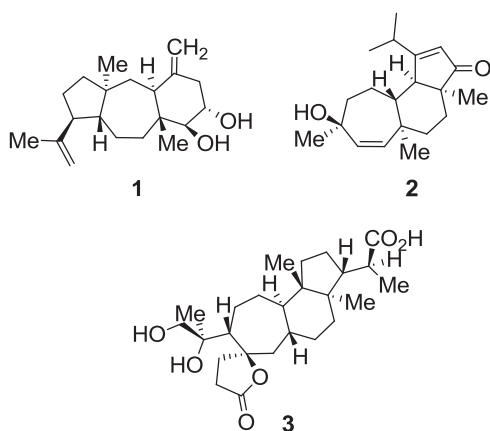


Fig. 1. Structures of terpenes with *trans*-fused seven-membered ring.

to construct 6/7 fused ring systems is to annulate six-membered ring on to prebuilt cycloheptenone derivatives through Diels–Alder reaction with appropriate dienes. However cycloheptenone derivatives are poor<sup>4</sup> dienophiles toward Diels–Alder reaction and produces *cis*-fused 6/7 ring systems. Thus to construct *trans*-fused 6/7 ring systems through Diels–Alder reaction, reactive *trans*-cycloheptenone derivatives need to be generated.

In 1965 Corey<sup>5</sup> and Eaton<sup>6</sup> independently demonstrated that cycloheptenone undergoes photo-isomerization to highly reactive non-isolable *trans*-cycloheptenone, which undergoes spontaneous Diels–Alder reaction when irradiated in presence of dienes to produce *trans*-fused cycloheptenone derivatives. Subsequently, in 1977 Hart et al.<sup>7</sup> demonstrated that benzocycloheptadienone when irradiated in furan led to products that could be attributed to arise through photo-isomerization to its *trans*-isomer followed by its thermal Diels–Alder reaction with furan. The photo-isomerization of cycloheptenone derivatives in conjunction with facile Diels–Alder reaction with appropriate dienophiles could be of great synthetic potential for synthesis of natural products having *trans*-fused 6/7 bicyclic ring system. However there is scarce report<sup>8–10</sup> that employs this sequence to make polycyclic fused and bridged ring systems. In all these investigations either cycloheptenone or cycloheptenone fused to an aromatic ring was employed.

We anticipated that a properly constructed bicycloheptenone derivative with a defined stereochemistry at the ring fusion when irradiated in presence of dienes would provide an expedient route for entry into the tricyclic compounds **1–3**. It may be noted that the

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stereocenters at the ring fusion may direct cycloheptenone derivatives to isomerize in two different modes that may give rise to two diastereomeric products. Indeed, Dorr and Rawal<sup>9</sup> observed that intramolecular photo-induced Diels–Alder reaction of cycloheptenone tethered to dienes at the allylic carbon produced adducts arising from both the possible photo-isomerized *trans*-cycloheptenone. On the contrary Davies et al.<sup>10</sup> demonstrated that photochemical Diels–Alder reaction of a cycloheptenone derivative embedded in a conformationally locked bridged ring system proceeded stereoselectively to lead to a single diastereomeric adduct. However, there is no report on the stereochemical outcome in photo-induced Diels–Alder reaction of fused bicycloheptenone derivatives.

We chose to investigate photo-isomerization of the cycloheptenone derivatives **4a, b** and Diels–Alder reaction of the isomerized *trans*-isomers with dienes that will lead to tricycles with *trans*-fused seven-membered ring. Photo-isomerization of **4a, b** may lead to the *trans*-cycloheptenone derivatives **5a, b** or **6a, b** or both (Fig. 2). Diels–Alder reaction of these *trans*-cycloheptenone derivatives with dienes thus may provide two diastereoisomeric adducts. In this paper we present the results of this investigation to determine the role of ring fusion stereochemistry in dictating the stereochemical outcome.

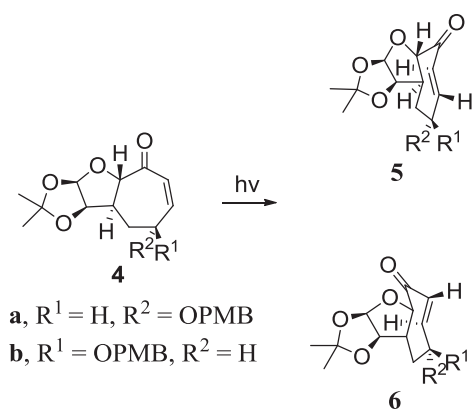
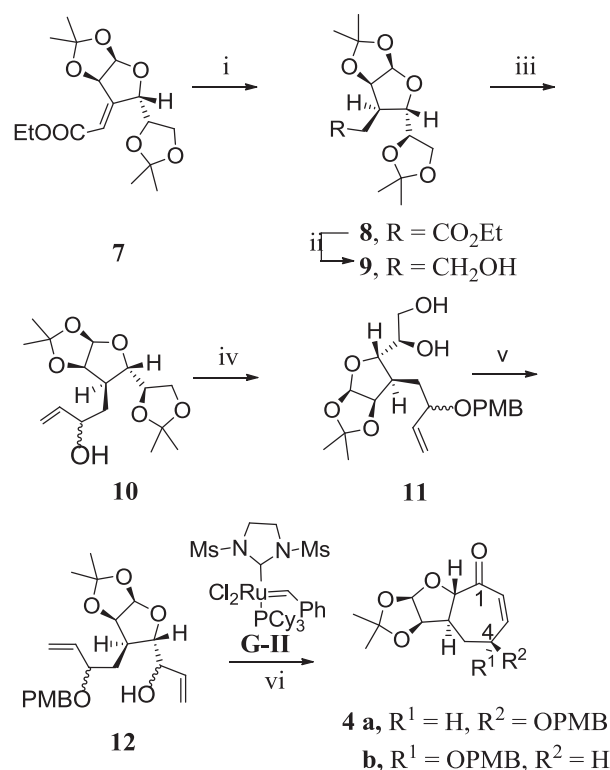


Fig. 2. Different modes of photo-isomerization of **4**.

## 2. Results and discussion

The cycloheptenone derivatives **4a, b** were prepared from the known unsaturated ester **7**<sup>11</sup> as shown in Scheme 1. Reduction<sup>12</sup> of the unsaturated ester **7** with sodium borohydride in presence of nickel chloride afforded the known<sup>13</sup> saturated ester **8** in 80% yield. Reduction of **8** with lithium aluminum hydride gave the known<sup>13</sup> alcohol **9** in 90% yield. This alcohol on Dess–Martin Periodinane (DMP) oxidation followed by addition of vinylmagnesium bromide to the resulting aldehyde led to an inseparable diastereoisomeric mixture of the alcohols **10** in 75% yield in ca. 1.7:1 ratio. Protection of the hydroxyl groups in **10** on treatment with sodium hydride and *p*-methoxybenzyl (PMB) chloride proceeded with concomitant deprotection of the 5,6-acetonide moiety to provide the PMB protected diol **11** in 80% yield as a diastereomeric mixture in about the same ratio as that of **10**. Sodium metaperiodate cleavage of the vicinal diol in **10** followed by addition of vinylmagnesium bromide to the resulting aldehyde afforded a diastereoisomeric mixture of the hydroxy compounds **12** in 70% yields. Treatment of **12** with Grubbs' second generation catalyst (**G-II**) in dichloromethane at rt led to smooth ring closure<sup>14</sup> resulting in a diastereoisomeric mixture of cycloheptenols, which on DMP oxidation provided a mixture of the cycloheptenone derivatives **4a, b** in 82% yield in ca. 1.7:1 diastereoisomeric ratio.



Scheme 1. Synthesis of cycloheptenones **4a, b**. Reagents and conditions: (i) NiCl<sub>2</sub>, NaBH<sub>4</sub>, MeOH, 80%; (ii) LiAlH<sub>4</sub>, 90%; (iii) (a) DMP, DCM; (b) CH<sub>2</sub>=CHMgBr, THF, –60 °C (75% in two steps); (iv) NaH, PMBCl, DMF, 0 °C, 80%; (v) (a) NaIO<sub>4</sub>, THF–H<sub>2</sub>O; (b) CH<sub>2</sub>=CHMgBr (70% in two steps); (vi) (a) **G-II**, DCM, 80%; (b) DMP, 85%.

When a solution of the diastereomeric mixture of cycloheptenone derivatives **4a, b** in DCM was irradiated in presence of furan, a mixture of the two diastereoisomeric adducts **13a** and **13b** was obtained (Scheme 2). Column chromatography of this mixture led to isolation of the adduct **13a** as a white crystalline solid, mp 115–117 °C. Inspection of the <sup>1</sup>H NMR spectrum of **13a** revealed that one of the two bridgehead hydrogens (C-5) in the oxa-bridge appeared as a singlet at  $\delta$  5.29 (*J* 0.0 Hz) while the other hydrogen (C-11) appeared at  $\delta$  5.70 as a doublet (*J* 3.5 Hz). It is well established<sup>15</sup> that in norbornene and oxa-norbornene derivatives, the bridgehead protons couple with the ring junction protons only when they are *exo* with a coupling constant of ca. 4 Hz. Comparison of the observed coupling constant values of the bridgehead protons in **13a** with the literature report indicated that the two hydrogens at the ring fusion (C<sub>5</sub>–H and C<sub>11</sub>–H) are *anti* to each other in the adduct **13a**. The structure of the adduct **13a** was finally confirmed by single-crystal X-ray diffraction (Fig. 3).<sup>16</sup> The C-10 epimeric adduct **13b** could not be isolated in pure form by column chromatography but its formation was indicated from <sup>1</sup>H and <sup>13</sup>C NMR spectra of the crude product mixture.

Thus during irradiation in presence of furan the cycloheptenone derivatives **4a, b** isomerized selectively to *trans*-cycloheptenones **6a, b**, which underwent Diels–Alder reaction with furan to form adducts **13a, b**.

The mixture of products **13a** and **13b** was treated with DDQ to remove the PMB group and the resulting hydroxy compounds were oxidized with DMP to produce the diketone **14**. This confirmed that adducts **13a** and **13b** arose from Diels–Alder reaction of the *trans*-cycloheptenones **6a** and **6b** formed in situ through photo-isomerization of the *cis*-cycloheptenones **4a** and **4b**, respectively. The *trans*-ring fusion in the diketone **14** was ascertained from comparison of the coupling constant of the oxa-bridgehead protons with those reported in literature<sup>15</sup> in analogous systems as well as

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