

# Tandem Pd-Catalyzed Carbonylation and Intramolecular Vinyl Allene Diels–Alder Reaction toward Galiellalactone Analogues

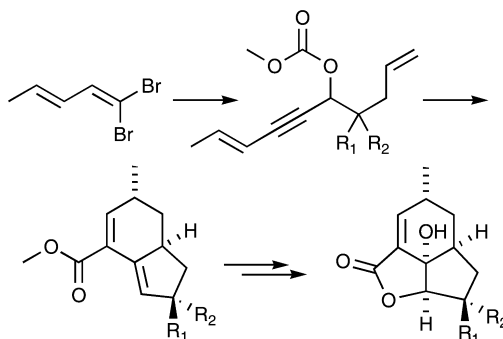
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## ABSTRACT



A novel route toward new galiellalactone analogues via a tandem palladium-catalyzed carbonylation and intramolecular Diels–Alder reaction of a dienyne carbonate is presented.

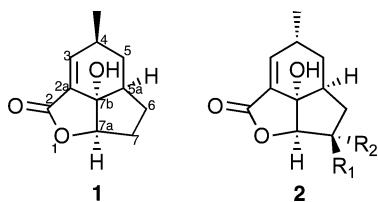
Galiellalactone (**1**) is a fungal metabolite that has been reported to be a potent inhibitor of IL-6 signaling mediated by STAT3,<sup>1</sup> a signal transducer and activator of transcription that is constitutively active in several forms of cancer. **1** has been shown to induce apoptosis in malignant hormone-refractory prostate cancer cell lines in vitro and to suppress prostate cancer cell xenograft growth in vivo.<sup>2</sup> It is believed to act as a direct STAT3 inhibitor by binding covalently to the protein and preventing its binding to DNA and the transcription of antiapoptotic genes.<sup>2</sup> Galiellalactone is consequently interesting for further development to a drug candidate, and although we previously have described an enantioselective synthesis of the natural product,<sup>3</sup> we were interested in developing a synthetic route that facilitates the

preparation of suitably substituted analogues. Preliminary SAR studies<sup>4</sup> have shown that the tricyclic structure, the oxygenation of the central carbon, and the  $\alpha,\beta$ -unsaturated lactone are absolutely essential for activity, while **1** is approximately equipotent to its epimer **2** (see Figure 1) as well as its enantiomer. A synthesis that permits the introduction of substituents at C4, C5, C6, and/or C7 (see Figure 1 for numbering) was therefore desired to further explore the SARs, and in this paper the introduction of alkyl/aryl substituents in position 7 is described.

The Diels–Alder reaction is one of the most versatile methods of preparing cyclohexene ring systems, and a tandem carbonylation/intramolecular vinyl allene Diels–Alder reaction, starting from relatively easily accessible dienyne

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(2) Hellsten, R.; Johansson, M.; Dahlman, A.; Dizely, N.; Sterner, O.; Bjartell, A. *Prostate* **2008**, 268, 269.  
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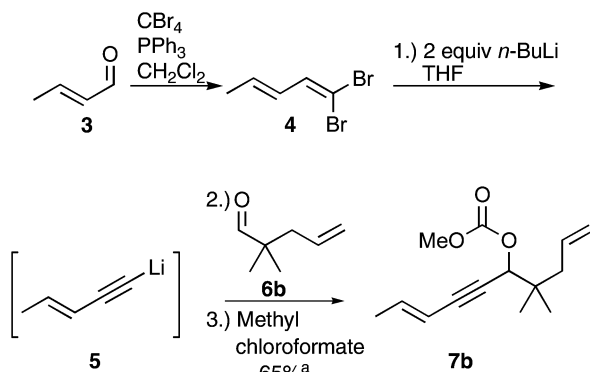
(4) (a) Johansson, M. Biosynthetic and Synthetic Studies of the Fungal Metabolite Galiellalactone, *Doctoral Thesis*, Lund, 2002. (b) Nussbaum, F.; Hanke, R.; Fahrig, T.; Benet-Buchholz, J. *Eur. J. Org. Chem.* **2004**, 13, 2783.



**Figure 1.** (–)-Galiellalactone (**1**), *epi*-galiellalactone (**2a**,  $R_1 = R_2 = H$ ), 7,7-dimethyl-*epi*-galiellalactone (**2b**,  $R_1 = R_2 = Me$ ), and 7-benzyl-*epi*-galiellalactone (**2d**,  $R_1 = Bn$ ,  $R_2 = H$ ).

carbonates, has previously been shown to be useful for the synthesis of a series of fused tetrahydroindenes.<sup>5</sup> As a tetrahydroindene is the key intermediate in the synthesis of galiellalactone analogues, and as we already have shown that the transformation of the tetrahydroindene **10a** to *epi*-galiellalactone **2a** is feasible,<sup>4a</sup> this strategy was investigated. The dienyne carbonate **7b** was prepared by subjecting crotonaldehyde **3** to the Corey–Fuchs procedure<sup>6</sup> to give 1,1-dibromo-1,3-pentadiene (**4**), which was transformed to the corresponding alkenynyl lithium salt (**5**) to which 2,2-dimethyl-4-pentalen (**6b**) was added. The alkoxide formed was treated with methyl chloroformate in situ to yield the dienyne carbonate **7b** (see Scheme 1). The reaction sequence

**Scheme 1.** Synthesis of Dienyne Carbonate **7b**



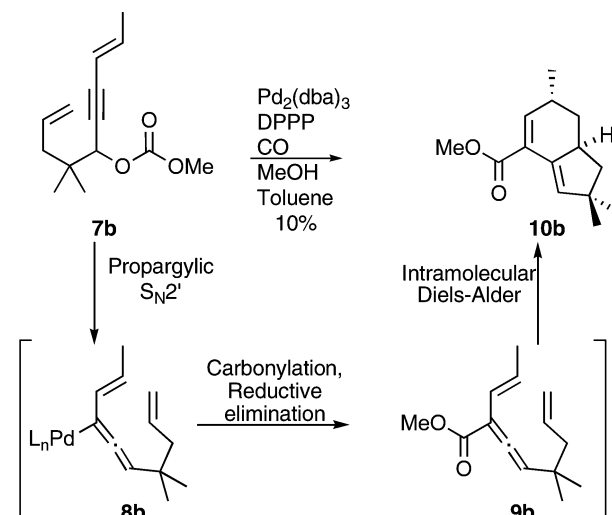
<sup>a</sup> Yield is based on **3**.

proceeded smoothly in up to at least 100 mmol scale, in good yields.

When carbonate **7b** was exposed to the conditions described by Mandai et al.<sup>5</sup> (see Scheme 2), the desired tetrahydroindene **10b** was obtained but only in 10% yield. This is in contrast to the high yields reported using cyclic dienyne carbonates.<sup>5</sup>

The poor yield of the tandem carbonylation/intramolecular Diels–Alder reaction prompted an optimization of the

**Scheme 2.** Tandem Carbonylation/Intramolecular Diels–Alder Reaction



catalyst system and reaction conditions, and this was carried out with **7b**. Changing the catalyst to  $Pd(OAc)_2$  resulted in only a minor improvement, while elevated temperature (100 °C) and methanol as solvent resulted in reduced yields. Exchanging the ligand for Xantphos resulted in acceptable yields (43%) at ambient pressure,<sup>7</sup> while  $Pd(OAc)_2$  and DPPP as the catalyst system using an autoclave at 5 bar of CO at 60 °C gave 17% of the product. Greatly improved yields (73%) were obtained using  $Pd(OAc)_2$  and DPPP under 5 bar of CO but at a lower temperature, 20 °C, while further increasing CO pressure decreased the yield. With  $Pd(OAc)_2$  and Xantphos as the catalytic system and elevated CO pressure (3 bar), the yield was only 3%. Under the conditions that gave the best results, the reaction was reproducible, also in larger scale (up to 60 mmol).

In **10b**, C4-Me and 5a-H are on the same face of the molecule, reversed compared to the natural product, although for our purposes this was not considered critical, as **1** and *epi*-galiellalactone (**2a**) display equal STAT3 activity. The relative orientation of the C4 methyl and the C5a hydrogen can be rationalized by the *exo* transition state of the Diels–Alder reaction, which is less strained than the *endo* as suggested by Okamura et al.<sup>8</sup>

New substituent(s) in position 7 require the use of different  $\alpha$ -substituted 4-pentenals (corresponding to **6b** in Scheme 1), and several dienyl carbonates were prepared and cyclized by the optimized procedure discussed above. The 4-pentenals were, when not commercially available, synthesized from the corresponding esters<sup>9</sup> by reduction with  $LiAlH_4$  and a subsequent Dess–Martin oxidation (see Supporting Information for details). The dienyne carbonates **7c–7e** were obtained as diastereomeric mixtures. The two diastereomers

(5) Mandai, T.; Suzuki, S.; Ikawa, A.; Murakami, T.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1991**, 32, 7687.

(6) (a) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 13, 3769. (b) Bialy, L.; Waldmann, H. *Chem.–Eur. J.* **2005**, 10, 2759. (c) Annabelle, L. K.; Shun, S.; Tykwinski, R. R. *J. Org. Chem.* **2003**, 68, 6810.

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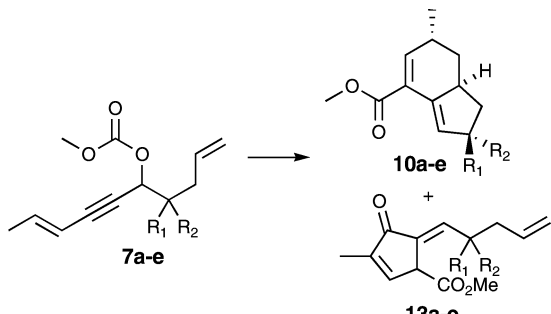
(8) Okamura, W.; Curtin, M. *Synlett* **1990**, 1, 1.

(9) Pour, M.; Spulak, M.; Balsanek, V.; Kunes, J.; Kubanova, P.; Buchta, V. *Bioorg. Med. Chem.* **2003**, 11, 2843.

of **7e** could be separated, but both were converted to 1:1 diastereomeric mixtures of **10e** when subjected to the tandem carbonylation/Diels–Alder reaction, suggesting that the initial oxidative addition of palladium is not stereoselective under these conditions. This lack of stereoselectivity is in agreement with what has been reported previously.<sup>8,10</sup>

Subjecting the carbonates **7a–7e** to the optimized Pd-catalyzed tandem carbonylation and intramolecular Diels–Alder conditions yielded the tetrahydroindenes **10a–10e** in reasonable to good yields (see Table 1). Major byproducts

**Table 1.** Yields of Desired Cyclization Product **10** and Undesired Cyclopentenone **13**, For the Dienes **7a–7e** (%)<sup>a,b</sup>



| entry | R <sub>1</sub> | R <sub>2</sub> | 10                             |                   | 13        |           |
|-------|----------------|----------------|--------------------------------|-------------------|-----------|-----------|
|       |                |                | yield [%]                      | yield [%]         | yield [%] | yield [%] |
| 1     | H              | H              | 36 ( <b>10a</b> )              | 14 ( <b>13a</b> ) |           |           |
| 2     | Me             | Me             | 73 ( <b>10b</b> )              | 13 ( <b>13b</b> ) |           |           |
| 3     | Ph             | H              | 46 ( <b>10c</b> ) <sup>c</sup> | 26 ( <b>13c</b> ) |           |           |
| 4     | Bn             | H              | 60 ( <b>10d</b> ) <sup>c</sup> | 22 ( <b>13d</b> ) |           |           |
| 5     | 1-Naph         | H              | 70 ( <b>10e</b> ) <sup>c</sup> | 26 ( <b>13e</b> ) |           |           |

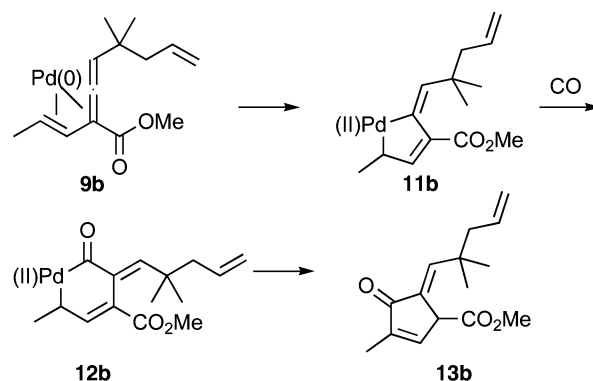
<sup>a</sup> Isolated yields after flash chromatography. <sup>b</sup> The reaction was carried out with 1 equiv of substrate, 0.2 equiv of Pd(OAc)<sub>2</sub>, and 0.2 equiv of DPPP, in toluene/methanol (2:1). <sup>c</sup> Obtained as 1:1 C7 diastereomeric mixtures.

of the reactions were the cyclopentenones **13a–13e**, presumably formed as shown in Scheme 3, through a competing five-membered palladacycle mechanism.<sup>11</sup>

A pronounced Thorpe–Ingold effect, favoring the Diels–Alder reaction of the *gem*-dimethyl substituted allene **9b**, was observed, as demonstrated by the high yield obtained for the synthesis of **10b** compared especially to **10a**. This carbonylation/Diels–Alder procedure provided us with a small library of tetrahydroindenes substituted at C7, of which **10c–10e** were obtained as diastereoisomeric mixtures, suitable for preparing analogues of **1**.

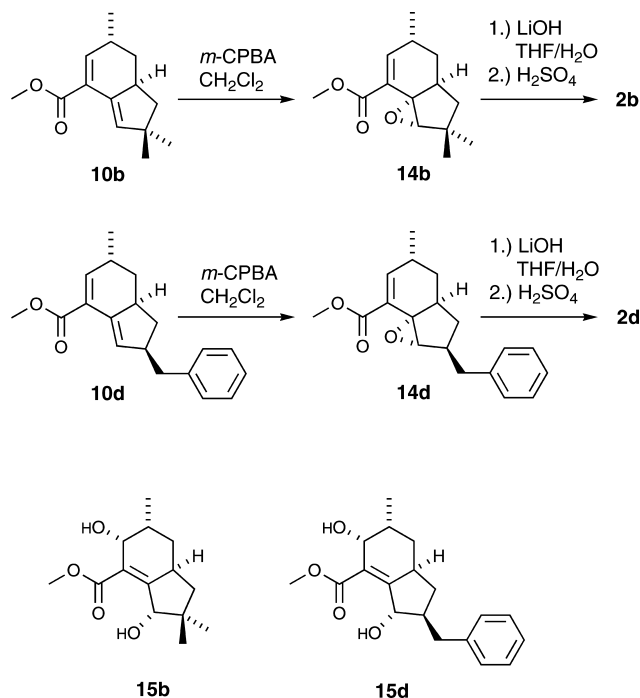
The transformation of the tetrahydroindenes **10a–10e** can in principle be carried out by the same procedure that was developed for the preparation of galiellalactone (**1**) and *epi*-galiellalactone (**2a**),<sup>4a,12</sup> i.e., an epoxidation of **10** to **14** followed by a hydrolysis of the ester and an opening of

**Scheme 3.** Dicarbonylation and Cyclization to Cyclopentenone **13b**



the epoxide by the free carboxylic acid function to form **2**. The diastereoselectivity of the epoxidation was expected to be high, favoring the desired epoxide **14**, and when the procedure was tested with tetrahydroindene **10b** the epoxide **14b** was obtained in 94% yield (Scheme 4).

**Scheme 4.** Synthesis of 7,7-Dimethyl-*epi*-galiellalactone (**2b**) and 7-Benzyl-*epi*-galiellalactone (**2d**)<sup>4a,12</sup>



The lactonization of epoxide **14b** to **2b** was surprisingly inefficient, as the yield was only 7% compared to 55 and 32%, respectively, when the corresponding reactions leading to **1** and **2a** were carried out. Lactonization of **14d** was more efficient providing **2d** with a yield of 25%; however, it is still obvious that the lactonization of these epoxide-esters is

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affected by substituents in position 7, and the conditions for this step consequently need to be further optimized. The major products in the lactonization of **14b** and **14d**, with the protocol developed to produce **1**, are the diols **15b** and **15d**. Although the isolated yield of **15b** and **15d** was low, no other side products from the reaction were observed, and significant losses of the byproduct are made during the chromatographic purification.

In conclusion, a new synthetic pathway that leads to novel 7-substituted galiellalactone analogues was developed, producing key intermediates in five steps starting from crotonaldehyde and a 2-substituted 4-pentenal. In principle, the corresponding route could be developed also to facilitate the inclusion of substituents in other positions. The galiellalac-

tone analogues will be assayed for their antitumor activity toward malignant hormone-refractory prostate cancer cell lines, and data will be presented in due course.

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**Supporting Information Available:** Experimental details, characterization data, and proton and carbon NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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