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

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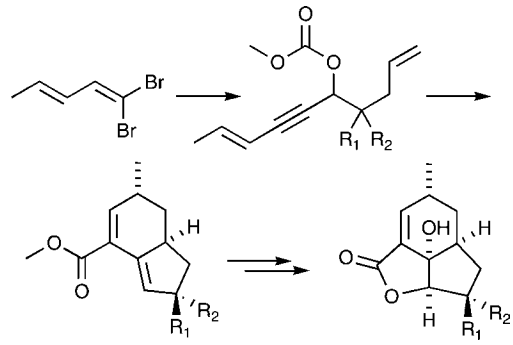
ABSTRACT



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,[1] 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.[2] 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 antiapoptopic genes.[2] Galiellalactone is consequently interesting for further development to a drug candidate, and although we previously have described an enantioselective synthesis of the natural product,[3] we were interested in developing a synthetic route that facilitates the preparation of suitably substituted analogues. Preliminary SAR studies[4] have shown that the tricyclic structure, the oxygenation of the central carbon, and the α,β-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

(1) Weidler, M.; Rether, J.; Anke, T.; Erkel, G. *FEBS Lett.* **2000**, 484.
(2) Hellsten, R.; Johansson, M.; Dahlman, A.; Dizeyi, N.; Sterner, O.; Bjartell, A. *Prostate* **2008**, *268*, 269.
(3) Johansson, M.; Sterner, O. *J. Antibiot.* **2002**, *55*, 663.
(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.

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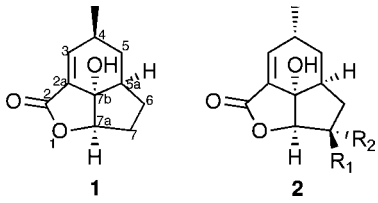
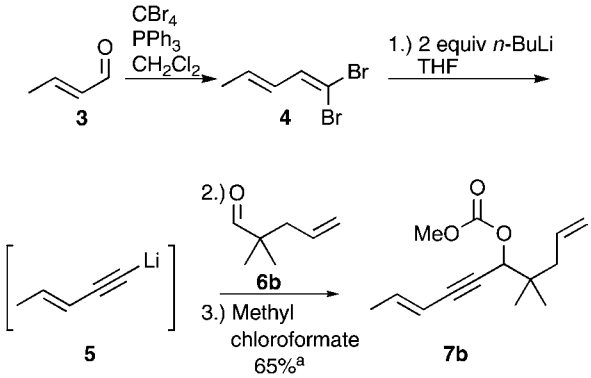


Figure 1. (−)-Galiellalactone (**1**), *epi*-galiellalactone (**2a**, $R_1 = R_2 = H$), 7,7-dimethyl-*epi*-galiellalactone (**2b**, $R_1 = R_2 = Me$), and 7-benzyl-*epi*-galiellalactone (**2d**, $R_1 = Bn$, $R_2 = H$).

carbonates, has previously been shown to be useful for the synthesis of a series of fused tetrahydroindenes.[5] 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,[4a] this strategy was investigated. The dienyne carbonate **7b** was prepared by subjecting crotonaldehyde **3** to the Corey−Fuchs procedure[6] 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-pentenal (**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**



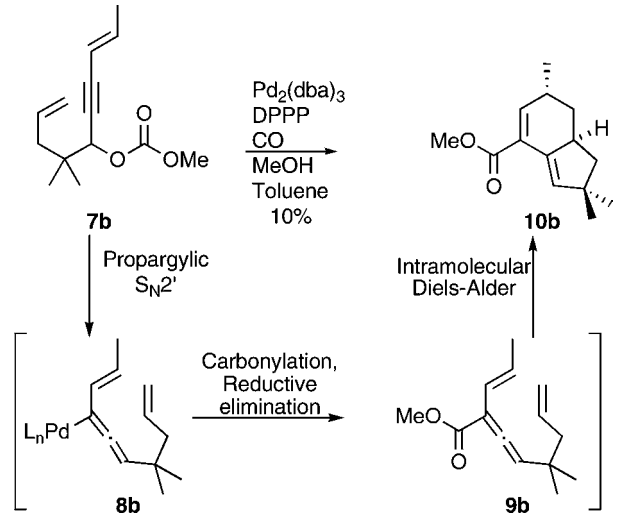
[a] Yield is based on **3**.

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.[5] (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.[5]

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,[7] 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 Xanthphos 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.[8]

New substituent(s) in position 7 require the use of different α-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[9] 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

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(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.

(7) Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7102.

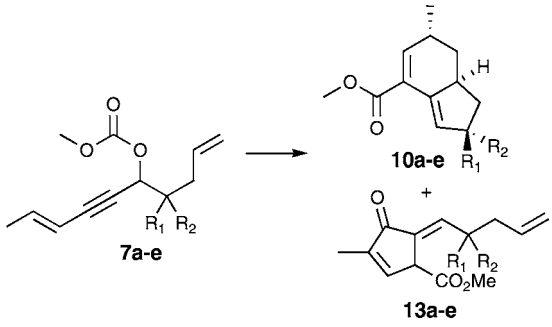
(8) Okamura, W.; Curtin, M. *Synlett* **1990**, *1*, 1.

(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.[8,10]

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 Cyclopentanone **13**, For the Dienynes **7a**−**7e** (%)[a,b]



			10	**13**
entry	R_1	R_2	yield [%]	yield [%]
1	H	H	36 (**10a**)	14 (**13a**)
2	Me	Me	73 (**10b**)	13 (**13b**)
3	Ph	H	46 (**10c**)[c]	26 (**13c**)
4	Bn	H	60 (**10d**)[c]	22 (**13d**)
5	1-Napth	H	70 (**10e**)[c]	26 (**13e**)

[a] Isolated yields after flash chromatography. [b] The reaction was carried out with 1 equiv of substrate, 0.2 equiv of $Pd(OAc)_2$, and 0.2 equiv of DPPP, in toluene/methanol (2:1). [c] 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.[11]

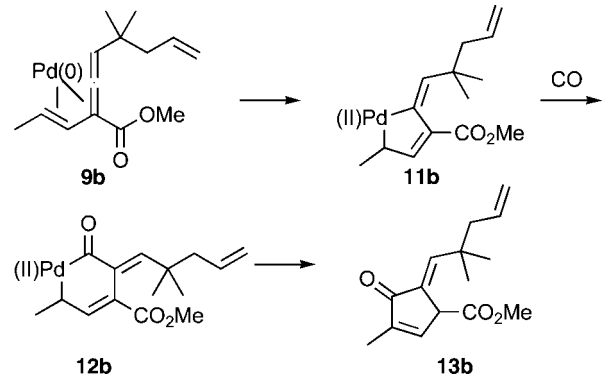
A pronounced Thorpe−Ingold effect, favoring the Diels−Alder reaction of the *gem*-dimethyl substituted allene **9b**, was observed, as demonstrated by the high yield obtained for the synthesis of **10b** compared especially to **10a**. This carbonylation/Diels−Alder procedure provided us with a small 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**),[4a,12] i.e., an epoxidation of **10** to **14** followed by a hydrolysis of the ester and an opening of

(10) (a) Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 2933. (b) Oishi, S.; Toda, A.; Takemoto, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **2002**, *67*, 1359.

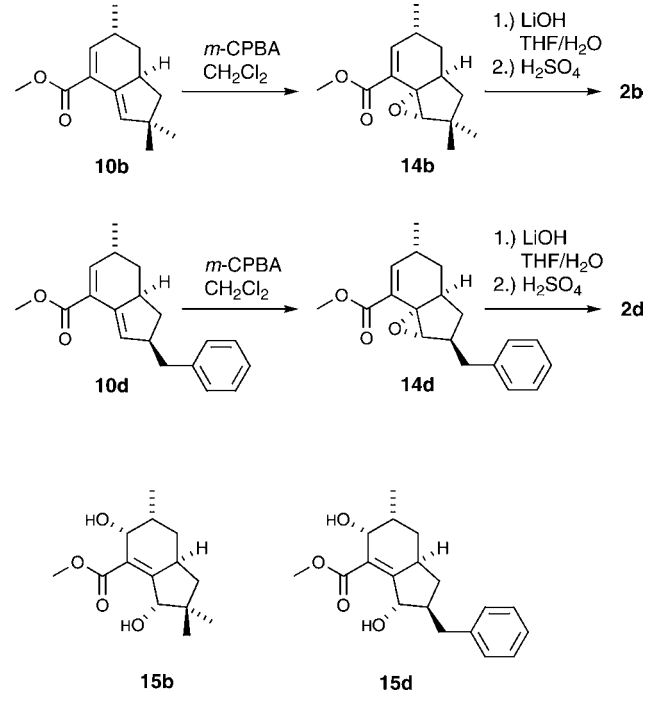
(11) (a) Mandai, T.; Tsuji, J.; Tsujiguchi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 5865. (b) Murakami, M.; Itami, K.; Ito, Y. *Organometallics* **1999**, *18*, 1326. (c) Hashmi, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590.

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**)[4a,12]



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

(12) Johansson, M.; Sterner, O. *Org. Lett.* **2001**, *3*, 2843.

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 galiellalactone 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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