Diels–Alder cycloaddition of *o*-quinonedimethides and alkylidene-5*H*-furan-2-ones: new and rapid access to lambertellol cores and arthrinone derivatives†

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An efficient synthesis of deoxy-lambertellols was reported through a highly chemo- and diastereoselective intermolecular Diels–Alder cycloaddition between *trans*-1,2-disiloxybenzocyclobutenes and 2-methylprotoanemonine. Such transformation with δ-substituted γ-alkylidenebutenolides, to prepare new analogues of these tricyclic spirolactones, which would be very difficult to prepare by other ways, was also studied.

Introduction

As predicted by Professor Otto Diels and his student Kurt Alder in 1928,[1] the [4+2] pericyclic reaction, has remained inescapable in the field of organic synthesis and particularly for the total synthesis of numerous natural products.[2] Since several years, our research group has been interested in the synthesis and reactivity of functionalized butenolides.[3] More particularly, γ-alkylidenebutenolides can be easily obtained in one step by a new procedure based on a free palladium Sonogashira coupling between a (*Z*)-3-iodoalkenoic acid and a terminal alkyne in presence of copper(I) salt.[4] Possessing an α,β-γ,δ unsaturated moiety, those lactones are interesting building blocks useful in various synthetic applications.[5] Contrary to their real synthetic potential, allowing to build stereoselectively a quaternary carbon at the spiro center, the γ,δ conjugate double bond of γ-alkylidenebutenolides has been scarcely used for that purpose. As the dienophile in Diels–Alder type reaction, the majority of examples reported in the literature deals with γ-alkylidenebutenolides without substitution in δ position leading to the formation of the corresponding spiro-cycloadduct.[6,7] The use of this exocyclic methylene in [4+2] cycloaddition was nicely illustrated in total synthesis of natural products or towards natural products core (Kijanolide core,[8] Chlorothricolide analog,[9] Andirolactone[10] and Abyssomicin C).[11] Only few examples were published with δ-substituted γ-alkylidenebutenolides[6e,12] such as the total synthesis of ircinianin.[13] Always in the field of Diels–Alder reaction, [4+2] reaction of benzocyclobutene derivatives remains one of the most powerful routes to prepare aromatic bicyclic compounds. Numerous polycyclic compounds of biological interest were prepared through a thermal ring opening, generating *o*-quinonedimethide followed by an inter- or intramolecular cycloaddition. This methodology was widely applied for the synthesis of natural products such as alkaloids, steroids, terpenoids or anthracyclines.[14] Among natural products with interesting biological activities, Lambertellols take the advantage to possess both aromatic bicyclic part and spirolactone moiety. They are known to cause mycoparasitism of *Lambertella sp*. against *Monilinia sp.* on apple fruit (Fig. 1).[15]

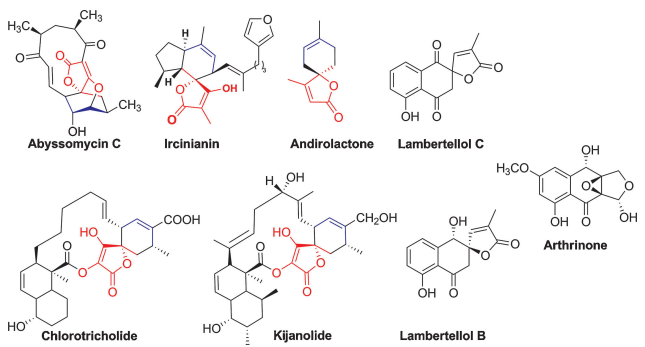
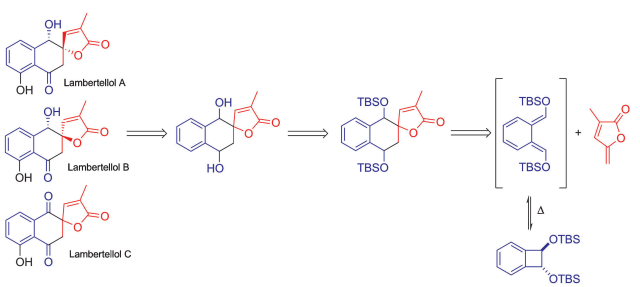


Fig. 1 Examples of natural products containing spirolactone moiety and/or naphthalen-1(4*H*)-one core.

Encouraged by the excellent reactivity of *trans*-1,2-disiloxybenzocyclobutenes **1** in [4+2] cycloaddition,[16] we have undertaken the study of intermolecular Diels–Alder reaction of **1** and methylene-5*H*-furan-2-one **2** as really convergent access to lambertellol backbone (Scheme 1). In this paper, we also studied such transformation with δ-substituted γ-alkylidenebutenolides in order to prepare new analogues of these tricyclic spirolactones which otherwise would be hardly accessible.



Scheme 1 Retrosynthetic scheme of Lambertellols backbone.

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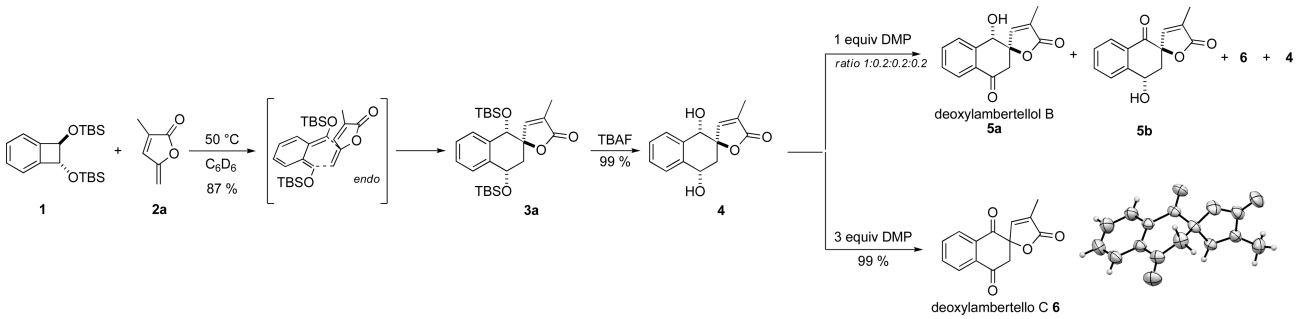


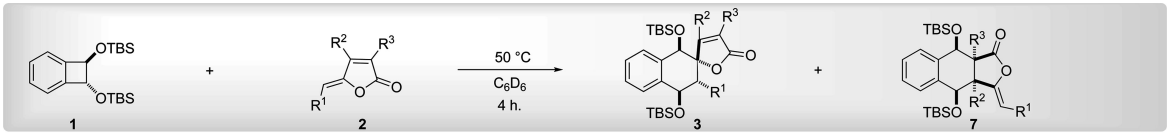
Scheme 2 Synthesis of deoxylambertellol C and B.

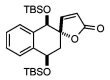
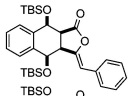
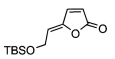
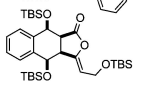
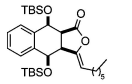
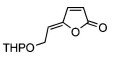
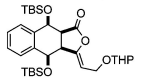
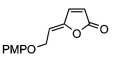
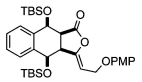
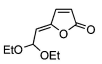
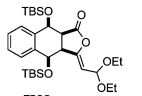
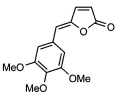
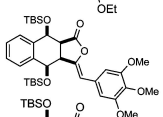
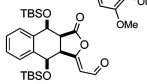
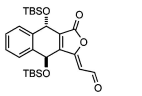
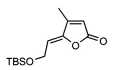
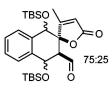
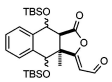
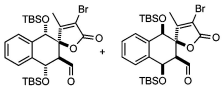
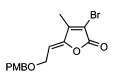
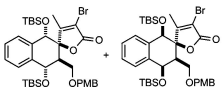
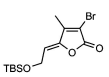
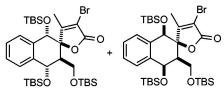
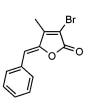
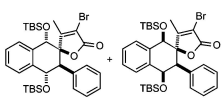
Results and discussion

Our investigation started with 1,2-*trans*-(*tert*-butyldimethylsiloxy)benzocyclobutene **1** and alkylidene butenolide **2a** (Scheme 2). Compound **1** was synthesized in gram scale according to the methods described by Liebeskind[17] and Danishefsky.[16f] Butenolide **2a** was prepared in two steps from acetone and pyruvic acid.[18,19] The aldolisation reaction followed by *in situ* crotonisation in acidic conditions furnished the desired lactol which is immediately dehydrated in presence of P_2O_5. At 50 °C in degassed benzene, [4+2] cycloaddition of **1** and **2a** occurred within 4 h, affording chemoselectively the desired spirolactone **3a** with complete *endo*-stereoselectivity in 87% yield. The stereochemistry of the cycloadduct was established without ambiguity by X-ray diffraction.[20] With the carbon skeleton of lambertellols in hand, we envisaged the synthesis of simplified deoxy-lambertellol. Spirolactone **3a** was then deprotected by reaction with tetrabutylammonium fluoride to afford diol **4** (quantitative yield) which was then oxidized using Dess Martin periodinane. Using one equivalent of Dess Martin periodinane furnished a 64/12/12/12 mixture of the sensitive and unstable deoxylambertellol B core **5a**, the corresponding regioisomer **5b**, **6** and **4** respectively whereas the use of an excess of oxidant gave the sensitive and unstable deoxylambertellol C **6** in quantitative yield.[21] Actually, the present method is largely competitive with the strategy employed for the total synthesis of lambertellols[22] and allows the construction of the lambertellol backbone in one step through a chemo- and diastereoselective [4+2] cycloaddition.

To further illustrate the synthetic use of the present method, we decided to evaluate the scope and limitations of the cycloaddition reaction by preparing more synthetic analogs of lambertellols. We have first evaluated the simplest alkylidene-5*H*-furan-2-one. In spite of the instability of protoanemonin **2b**,[18,23] we were pleased to find (Scheme 3, entry 1) that **2b** reacts smoothly to give diastereoselectively a 2/1 mixture of tricyclic-spirolactone **3b** and tricyclic fused product **7b** respectively (47% yield). These results were slightly different from Ortuño and Ventera's results in which only the *spiro*-cycloadducts were obtained using buta-1,3-diene derivatives.[6,7] In view of the divergent chemoselectivities observed in the Diels–Alder reaction of *trans*-1,2-disiloxybenzocyclobutenes **1**, several δ-substituted γ-alkylidenebutenolides **2c–i** were submitted to the cycloaddition reactions conditions (Scheme 3). These lactones were prepared by tandem free palladium Sonogashira cross-coupling/oxacyclisation reactions between acid (*Z*)-3-iodopropenoic acids and terminal alkynes.[4] Results obtained from [4+2] cycloaddition reaction between **1** and **2c–k**, are assembled in Scheme 3 (entries 2–10). Whatever the substitution pattern (alkyl, aryl, CH_2OPG, $CH(OEt)_2$), all reactions gave similar results, affording cycloadducts **7c–i** in excellent yield. The cycloaddition reactions take place only at the endocyclic double bond with an *endo*-stereoselectivity. The diastereoselectivity of the reaction was confirmed by X-ray diffraction studies realized on **7c**.[24] When a second isomer (up to 7%), in mixture with the first one, was detected, it was difficult to exactly determine its origin: it could be derived from the *E*-isomers of the starting lactone, from a radical mechanism or from an *exo*-approach. Even when the expected spiro-cycloadduct are not obtained, the alternative cycloadducts **7c–i** present an interesting naphtofuranone structure which can be found in arthrinone[25] derivatives (Fig. 1). The latter compounds exhibits pronounced biological (mainly antibacterial and antifungal) activities. Limited cytotoxicity was also expressed towards the NCI-60 tumour cell line.[26] To compare with previous lactones substituted with electron donating group, the reaction was performed with alkylidenebutenolide possessing an electron deficient exocyclic double bond. Lactone **2j** (Scheme 3, entry 9), prepared by acidic hydrolysis of the acetal function of **2h**, was heated in benzene with **1**. However, in this case cycloaddition reaction equally occurred at the endocyclic double bond to give the fused tricyclic aldehyde **3j** as a single diastereomer. Addition of $BF_3{\cdot}OEt_2$, to drive the reaction to the exocyclic double bond, did not allow any cycloadduct and only degradation of starting materials was observed.

The cycloaddition carried out with lactone **2k** (Scheme 3, entry 10), sterically and electronically hindered at the α position, took place only on the endocyclic double bond and furnished, after purification on silica gel, a 78 : 22 mixture of inseparable diastereomers dehydrohalogenated naphtofuranone.[27] The stereochemistry observed for the major diastereomer **7k** differed from that of the other cycloadducts **7b–j**. This last result led us to conclude that, in this case, the thermal cycloaddition could involve a biradical mechanism[6h,I] or **7k** could easily undergo epimerization at the allylic OTBS position. Unfortunately, when alkylidenebutenolides **2l–m** (Scheme 3, entries 11–12) substituted at the β-position by a methyl group were used as dienophiles, no [4+2]-cycloaddition reactions occurred. In order to favour the cycloaddition reaction, we decided to install an electron withdrawing group onto the exocyclic double bond of the lactone (Scheme 3, entry 13). So using lactone **2n** bearing an aldehyde function, the cycloaddition reaction afforded a 59 : 31 : 10 mixture of three



entry			yield (%)	3		7	dr
1	**2b**		47		+ 2:1		
2	**2c** (*Z*/*E* : 100/0)		78	--			100:0
3	**2d** (*Z*/*E* : 94/6)		78	--			94:6
4	**2e** (*Z*/*E* : 92/8)		72	--			96:4
5	**2f** (*Z*/*E* : 94/6)		76	--			nd
6	**2g** (*Z*/*E* : 100/0)		81	--			94:6
7	**2h** (*Z*/*E* : 100/0)		75	--			100:0
8	**2i** (*Z*/*E* : 100/0)		83	--			93:7
9	**2j** (Z/E : 100/0)		99	--			100:0
10	**2k** (Z/E : 100/0)		48	--			78:22
11	**2l** (Z/E : 100/0)			--		--	
12	**2m** (Z/E : 100/0)			--		--	
13	**2n** (Z/E : 100/0)		65	 75:25	+		56:44
14	**2o** (Z/E : 100/0)		75 77:18:1:4		+ third diastereomer		
15	**2p** (Z/E : 100/0)		57	 73:27		--	
16	**2q** (Z/E : 100/0)		70	 55:45		--	
17	**2r** (Z/E : 100/0)		55	 75:20:5	+ third diastereomer	--	

Scheme 3 Study of intermolecular Diels–Alder reaction.

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[4+2]-cycloadducts: the naphtofuranone **7n** (obtained as 1.3/1 mixture of two diastereomers), the corresponding spirolactone **3n** (obtained as 1/0.33 mixture of two diastereomers) and the product (obtained as single diastereomer)[28] formed by hetero Diels–Alder reaction onto the aldehyde function. The chemoselectivity of the cycloaddition reaction can be reversed (Scheme 3, entries 14) when the reaction was performed with lactone **2o** having a halogen atom at the α-position of the carbonyl function of the lactone. When the endocyclic double bond is tetrasubstituted, the cycloaddition reaction afforded, in 75% yield, a 96 : 4 mixture of spirolactone **3o** and naphtofuranone **7o** respectively.[29] **3o** was obtained in 80 : 18 : 2 mixture of three diastereomers, the two major corresponding in a classical pericyclic mechanism (*endo*- and *exo*-approach).[30] Contrary to the reaction conducted with lactone **2n**, no hetero cycloadduct was observed using aldehyde **2o**. Replacement of the aldehyde function at the δ position by OPMB, OTBS or phenyl groups (lactones **2p–r**) does not change the chemoselectivity of the reaction. The [4+2] cycloaddition occurs only at the exocyclic double bond to give the corresponding spiro-cycloadducts **3p–r** consisting of mainly two diastereomers in variable relative amounts. The presence of a bromine atom is a very good opportunity to introduce other substituents (CC, CO or CN bonds formation) and to have an access to more functionalized spirolactones. The reduction of carbon brome bond would be also very facile furnishing in two steps the spiro-products, impossible to prepare by other ways or with other δ-substituted alkylidenebutenolides.

Conclusion

In summary, we have reported a new highly selective and convergent approach to arthrinone or lambertellol core through an intermolecular Diels–Alder reaction with *trans*-1,2-disiloxybenzocyclobutenes and γ-alkylidenebutenolides. The chemoselectivity of the cycloaddition reaction can be modulated by ring substitution onto the starting lactone. Total syntheses of lambertellol B and C are in progress and will be reported in due course.

Acknowledgements

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Notes and references

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29 Cycloaddition performed with lactone acetal, precursor of lactone aldehyde **2p** led to the formation of the corresponding spiro-cycloadduct. Unfortunately, the acetal function was too sensitive and up to 40% of deprotected aldehyde **3p** was recovered after purification on neutralized silica gel.
30 The stereochemistry of the third diasteromer was not assigned.

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