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

Romain Blanc, Virginie Héran, Raphaël Rahmani, Laurent Commeiras* and Jean-Luc Parrain*

An efficient synthesis of deoxy-lambertellols was reported through a highly chemo- and diastereo-selective intermolecular Diels–Alder cycloaddition between trans-1,2-disiloxybenzocyclobutenes and 2-methylprotono-anemonine. Such transformation with δ-substituted γ-alkylidenebutenolides, to prepare new analogues of these tricyclic spiriolactones, 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(ii) 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-alkylidenbutenolides 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 Andirolac tone10 and Abyssomycin C).11 Only few examples were published with δ-substituted γ-alkylidenebutenolides12,13 such as the total synthesis of irciniann.14 Always in the field of Diels–Alder reaction, [4+2] reaction of benzo[cyclobutene 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.15

Among natural products with interesting biological activities, Lambertellols take the advantage to possess both aromatic bicyclic part and spiriolactone moiety. They are known to cause mycoparasitism of Lambertella sp. against Monilinia sp. on apple fruit (Fig. 1).16

Encouraged by the excellent reactivity of trans-1,2-disiloxybenzocyclobutenes 1 in [4+2] cycloaddition,17 we have undertaken the study of intermolecular Diels–Alder reaction of 1 and methylene-5H-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 spiriolactones which otherwise would be hardly accessible.

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

Scheme 1 Retrosynthetic scheme of Lambertellols backbone.
Results and discussion

Our investigation started with 1,2-trans-(tert-butylidin-
ethylsiloxyl)benzocyclobutene 1 and alkylidene butenolide 2a (Scheme 2). Compound 1 was synthesized in gram scale according to the methods described by Liebeskind and Danishefsky. Butenolide 2a was prepared in two steps from acetone and pyruvic acid. The aldolisation reaction followed by in situ protonation in acidic conditions furnished the desired lactol which is immediately dehydrated in presence of P(O)Cl. 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. With the carbon skeleton of lambertellols in hand, we envisaged the synthesis of simplified deoxy-lambertellol B core 5a, the corresponding regiosomer 5b, 6 and 4 respectively whereas the use of an excess of oxidant gave the sensitive and unstable deoxy-lambertellol C 6 in quantitative yield. Actually, the present method is largely competitive with the strategy employed for the total synthesis of lambertellols and allows the construction of the lambertellol backbone in one step through a chemo- and diasteroselective [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 the 1,2-trans-(tetr-alkylidino)butenolides and to expand the scope of this methodology to more synthetic analogs of the alkylidenebutenolides possessing an electron deficient exocyclic double bond. Lactone 2 (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. Another method of preparation for the formation of an electron deficient oxycyclohexene double bond, Lactone 2k–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 3-iodopropenoic acids and terminal alkynes. 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$_2$OPG, CH(OE)$_2$), 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 diasteroselectivity of the reaction was confirmed by X-ray diffraction studies realized on 7c. 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 naphthofuranone structure which can be found in arthrinone derivatives (Fig. 1). The latter compounds exhibit pronounced biological (mainly antibacterial and antifungal) activities. Limited cytotoxicity was also expressed towards the NCI-60 tumour cell line. 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. 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$_3$·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 naphthofuranone. 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 or a biradical mechanism 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
Scheme 3  Study of intermolecular Diels–Alder reaction.
the cycloaddition reaction afforded, in 75% yield, a 96:4 mixture and course. by ring substitution onto the starting lactone. Total syntheses of the cycloaddition reaction can be reversed (Scheme 3, entries 20) lactone or CN bonds formation) and to have an access to more is a very good opportunity to introduce other substituents (CC, 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 alkylidenobutenolides.

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-disiloxycyclobutenes and γ-alkylidenobutenolides. 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.

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Notes and references

22 CCDC 773864 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Even if one ‘TBS’ moiety was found to be disordered for compound 3m and was refined on 2 sites of occupancy equal to 0.8 and 0.2 respectively, the relative stereochemistry can be established without ambiguity. See supporting information.
23 CCDC 778187 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Even if both ‘TBS’moeities were found to be disordered for compound 7c, the relative stereochemistry can be established without ambiguity. See supporting information.

27 $^1$H NMR spectrum of the crude product revealed the presence of a 1/0.9 mixture of the deshydrohalogenated and non-deshydrohalogenated naphthofurane respectively.

28 The stereochemistry was not assigned. For hetero Diels–Alder reactions with o-quinonedimethyldiethylenetriamine see ref. 16e.

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.