



HAL
open science

First studies directed towards the diastereoselective synthesis of the BCD tricyclic core of brownin F

Fabien Rodier, Jean-Luc Parrain, Gaëlle Chouraqui, Laurent Commeiras

► To cite this version:

Fabien Rodier, Jean-Luc Parrain, Gaëlle Chouraqui, Laurent Commeiras. First studies directed towards the diastereoselective synthesis of the BCD tricyclic core of brownin F. *Organic & Biomolecular Chemistry*, 2013, 11, pp.4178-4185. 10.1039/c3ob40363g . hal-00861693

HAL Id: hal-00861693

<https://hal.science/hal-00861693v1>

Submitted on 13 Sep 2013

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

First studies directed towards the diastereoselective synthesis of the BCD tricyclic core of brownin F†

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 4178Received 19th February 2013,
Accepted 24th April 2013

DOI: 10.1039/c3ob40363g

www.rsc.org/obc

Fabien Rodier, Jean-Luc Parrain, Gaëlle Chouraqui* and Laurent Commeiras*

The BCD tricyclic core of brownin F was prepared in eight synthetic operations for the first time. Our synthesis features a diastereo-, chemo- and regioselective intramolecular [3 + 2] cycloaddition between a cyclic carbonyl ylide and a γ -alkylidenebutenolide.

Introduction

The Rutaceae thorn bush *Harrisonia brownii* Juss has long been recognised for its medicinal properties. Widespread throughout South-East Asia, its roots have been used in folk medicine for the treatment of dysentery and cholera. Several limonoids, known as brownins A–H, have been isolated from the wood and bark of this plant and believed to be the source of this bioactivity.¹ Even though they were isolated nearly twenty years ago, studies directed towards the total synthesis of molecules from the brownins family have never been reported.

From a structural perspective, brownin F (1) is a highly oxygenated tetranortriterpene featuring a unique tetracyclic core decorated with a spirobicyclic system and a bridged cyclic acetal (Fig. 1). Embedded within this compact framework are eight stereocentres, five of which are tetrasubstituted. The impressive structural complexity of brownin F (1), especially its challenging (5,7) bicyclic motif, made it of particular interest to us.

Accordingly, we recently reported an efficient and selective method for accessing highly oxygenated rigid polycyclic systems containing a [6.4] spiro motif through a rhodium mediated [3 + 2] cycloaddition² using a γ -alkylidenebutenolide as a dipolarophile partner. The γ -alkylidenebutenolide precursor has been used on several occasions within our group for the construction of complex structures presenting a spiro-centre through the Diels–Alder³ or domino reactions.⁴

Herein we wish to describe a diastereoselective approach towards the synthesis of the tricyclic skeleton of brownin

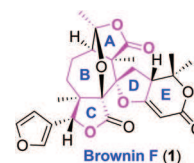
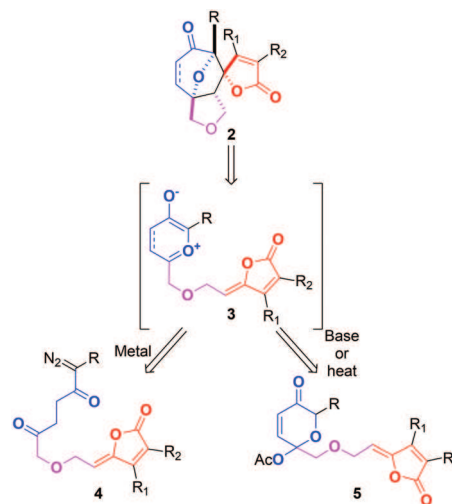


Fig. 1 Natural product brownin F (1).



Scheme 1 The [3 + 2] cycloaddition strategy.

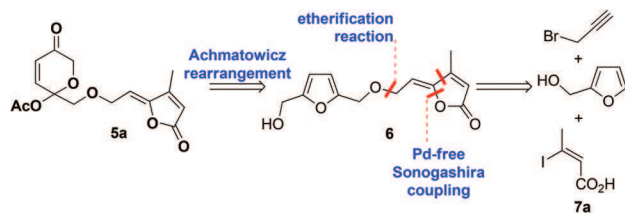
F 1 utilising an intramolecular [3 + 2] cycloaddition methodology^{2,5} between a cyclic carbonyl ylide and a γ -alkylidenebutenolide.

To this end, two strategies were at our disposal based upon the trapping of the carbonyl ylide species 3 with a suitable dipolarophile to access the seven-membered ring (Scheme 1). The carbonyl ylide could be generated *in situ via* either metal-catalysed decomposition of α -diazoketones containing another carbonyl group 4⁶ or upon exposure of acetoxy pyranones 5 to heat and/or the base.⁷ We decided to explore the feasibility of

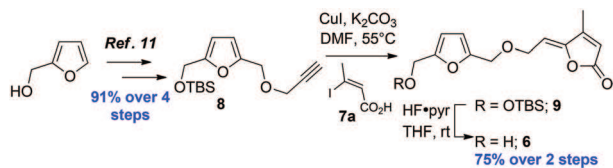
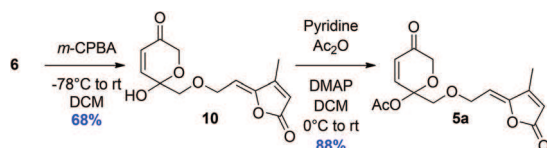
Aix Marseille Université, CNRS, iSm2 UMR 7313, 13397 Marseille cedex 20, France.
E-mail: gaëlle.chouraqui@univ-amu.fr, laurent.commeiras@univ-amu.fr;

Fax: (+33)-(0)4 91 28 91 87; Tel: (+33)-(0)4 91 28 91 88

† Electronic supplementary information (ESI) available: Experimental procedures and analytical data for all novel compounds and theoretical results. CCDC 906866 and 907998. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob40363g



Scheme 2 Retrosynthetic analysis.

Scheme 3 Preparation of the γ -alkylidenebutenolide **6**.Scheme 4 Preparation of the acetoxy pyranone **5a**.

both pathways, commencing with the acetoxy pyranone strategy.

Results and discussion

The key components of our retrosynthetic plan consist of an Achmatowicz rearrangement⁸ of 2-furylcarbinol **6** to access the acetoxy pyranone **5a**, a palladium-free Sonogashira coupling for the formation of the γ -alkylidenebutenolide,⁹ and an etherification reaction to couple the cyclisation partners. (*Z*)-Iodoacrylic acid¹⁰ **7a** and commercially available propargyl bromide and furfuryl alcohol would thus serve as the key building blocks for this approach (Scheme 2).

Our synthetic efforts began with the preparation of the 2,5-bis ether furan **8** in four steps according to a known procedure from commercially available furfuryl alcohol¹¹ (Scheme 3). Subsequently, the use of the Pd free Sonogashira coupling reaction developed in our laboratory,⁹ as a means to achieve the formation of the γ -alkylidenebutenolide, proved successful and provided the desired lactone. Deprotection of the silyl ether then afforded the required alcohol **6** in 75% yield (over 2 steps) in readiness for the oxidative rearrangement.

Achmatowicz rearrangement⁸ was achieved through treatment of **6** with *m*-CPBA in dichloromethane to give the corresponding hemiacetal **10** in 68% yield (Scheme 4). Protection of the latter provided acetoxy pyranone **5a** in 88% yield.

With the desired functionality installed, we were poised to evaluate the key [3 + 2] cycloaddition. Unfortunately our first

Table 1 [3 + 2] Cyclisation

Solvent	Conversion ^a
Toluene	No reaction
Dichloromethane	55%
Acetonitrile	100%

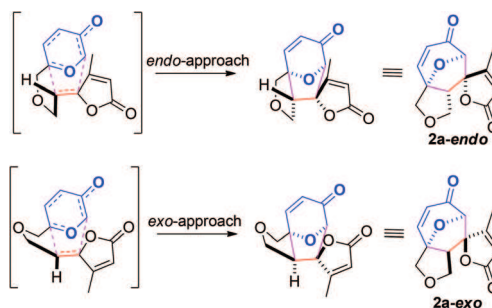
^a Conversion measured by NMR.

attempt, carried out in the presence of triethylamine in toluene, failed to furnish the desired cycloadduct, and the starting material remained unchanged even after six hours at reflux (Table 1). It was soon apparent that the outcome of the reaction was closely related to the nature of the solvent,¹² where the more polar solvent dichloromethane enabled a 55% conversion in favour of the expected polycyclic structure **2a**. Following this trend, complete conversion was observed in acetonitrile. Polycyclic compound **2a** was obtained as a single diastereomer in each case, validating this strategy in which four stereocentres were created (including two tetrasubstituted carbons) in a fully chemo-, regio- and diastereoselective manner. It should be noted that at this stage of the study, we were unable to determine the relative configuration of the four created stereocentres.

Our group has previously demonstrated that the diastereoselectivity of the intramolecular Rh-mediated [3 + 2] cycloaddition between a γ -alkylidenebutenolide and a carbonyl ylide is strongly dependent on the length of the tether between the cyclisation partners.² The approach was found to be an *endo* one when an all carbon five-membered ring is formed.

To gain further insight into the formation of **2a**, we decided to apply DFT calculations to determine whether the total diastereoselectivity observed here was the result of an *endo* (**2a-endo**) or an *exo* (**2a-exo**) approach (Scheme 5).

Calculations were performed at the B3LYP level (as implemented in the Gaussian09 program package) and the 6-311G++(d,p) basis set.¹³ Reported energies were computed as



Scheme 5 Plausible transition states for the intramolecular [3 + 2] cycloaddition.

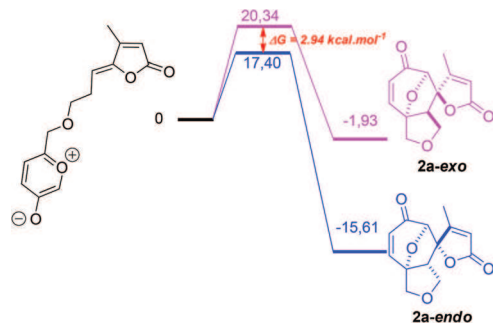
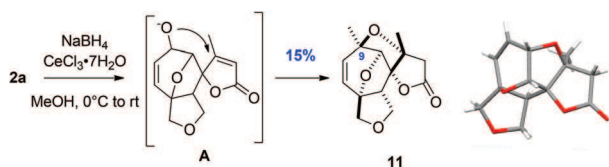


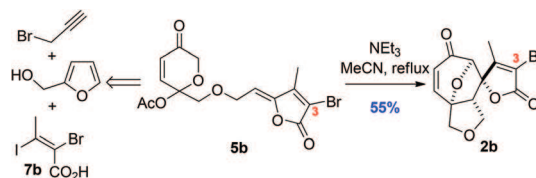
Fig. 2 Energy profile of the intramolecular [3 + 2] cyclisation step.

single point energy (ZPE) obtained at the geometry optimisation level. Each stationary point was adequately characterised by normal coordinate analysis (no imaginary frequencies for an equilibrium structure and one imaginary frequency for a transition state structure). In each case the cycloaddition step was found to be exothermic *via* a transition state of at least 17.4 kcal mol⁻¹ (Fig. 2). Notably, the transition state leading to the *exo* adduct **2a-exo** is around 3 kcal mol⁻¹ higher in energy than the transition state leading to the *endo* one. Inspection of the possible transition states and products energy levels therefore suggested that the compound experimentally isolated should correspond to the structure **2a-endo**, from both a thermodynamic and a kinetic point of view.

Despite the success of this cyclisation, a number of drawbacks remained. Besides the pervading relative stereochemical ambiguity, the cycloadduct **2a** also proved to be rather unstable under various conditions employed for its purification (flash chromatography on neutralised (Et₃N) silica gel or florisil). The inherent cyclic strain due to the presence of the conjugated double bond in the bicyclic seven-membered ring might be responsible for the poor stability observed. Williams *et al.* have reported that the enone system contained in the bicyclo[5.4.0]undecane structure is a particularly active electrophile and reacts readily with a range of nucleophiles.¹⁴ Initially, reduction of the enone system and therefore sp² to sp³ rehybridisation of carbon C-9 was considered in order to release this cyclic strain (Scheme 6). When ketone **2a** was subjected to reduction under Luche conditions (sodium borohydride, heptahydrate cerium(III) chloride in methanol) however, the expected alcohol was not observed but 15% of pentacyclic structure **11** was instead isolated as a single diastereomer (the low yield is related to the poor stability of the starting material **2a**). This polycyclic scaffold **11** appears to be the result of the intermediate C-9 alkoxide **A** undergoing an oxa-Michael addition upon the lactone.



Scheme 6 Luche reduction.¹⁵



Scheme 7 Synthesis of functionalised cycloadduct **2b**.

Fortunately, compound **11** turned out to be crystalline and its relative stereochemistry was thus unambiguously secured through X-ray crystallographic analysis,¹⁶ proving, in agreement with the computational study, the *endo* approach for the previous [3 + 2] cyclisation and confirming the relative configuration as the one drawn in **2a-endo**.

We next aimed to change the nature of the γ -alkylidenebutenolide. A bromine substituent was introduced in order to allow further functionalisation at carbon C-3 (Scheme 7). Acetoxypyranone **5b** was prepared in an analogous manner to that described for **5a**.¹⁷ One major advantage of our Pd-free Sonogashira coupling reaction is that no further side reaction (including oxidative addition on the remaining α -halogen or β -elimination) is observed when an $\alpha\beta$ -dihaloalkenoic acid such as **7b** is used in the process.¹⁸ Once again the base promoted cyclisation proceeded smoothly with total conversion, regio-, chemo- and diastereoselectivity, and cycloadduct **2b** now proved somewhat more stable as it could be purified by flash chromatography on silica gel and isolated in 55% yield. The relative stereochemistry was assigned by analogy with previous results and associated DFT calculations.¹⁹

Despite the issue of instability, our highly convergent synthetic strategy represents an efficient means of preparing the tricyclic core of brownin F. The intramolecular [3 + 2] cycloaddition between a γ -alkylidenebutenolide and an oxidopyrylium ylide enables efficient creation of four stereocentres with the required relative stereochemistry of the natural product at C-1, C-13 and C-14 in a single synthetic operation (Fig. 3). In addition, further functionalisation at C-3 is now enabled by virtue of the introduction of the vinyl bromide prior to cyclisation.

We next turned our attention to the metal-mediated cyclisation strategy. Such an approach might lead to more stable cycloadducts (avoiding the formation of the double bond in the seven-membered ring) and would allow the introduction of an additional tetrasubstituted stereocentre at C-10.

As outlined retrosynthetically in Scheme 8, preparation of the cyclisation precursor **4a** would involve a copper mediated lactonisation reaction to form the γ -alkylidenebutenolide

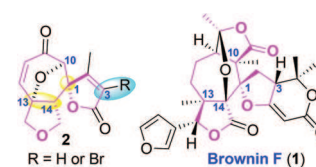
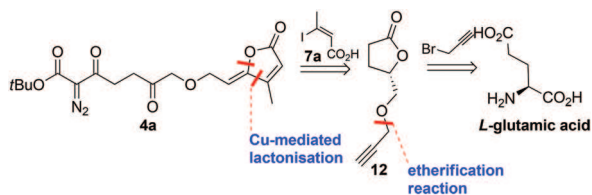
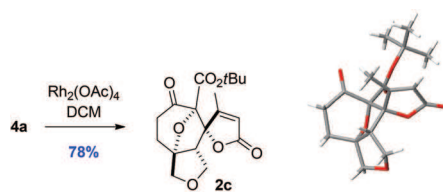


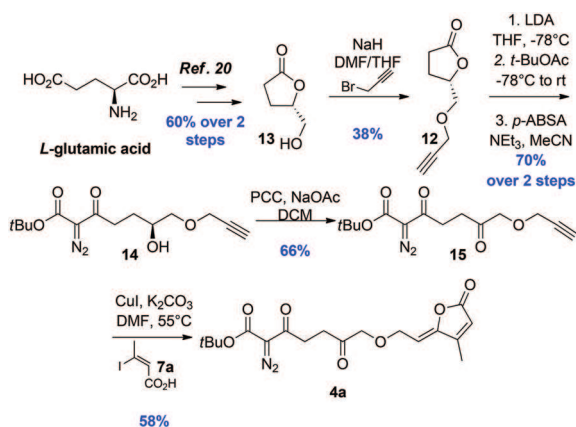
Fig. 3 The tricyclic core of brownin F.



Scheme 8 Retrosynthesis analysis for diazo derivative 4a.



Scheme 10 Rh-mediated [3 + 2] cyclisation.

Scheme 9 Synthesis of α -diazoketone 4a.

followed by an etherification reaction. Following these disconnections, the simple segments (*Z*)-iodoacrylic acid 7a and commercially available *L*-glutamic acid and propargyl bromide were proposed for the construction of 4a.

Guided by this strategy, we began our synthesis with the preparation of lactone 13 in two steps from glutamic acid, according to a reported procedure (Scheme 9).²⁰ Etherification of 13 with propargyl bromide provided lactone 12, which then underwent opening with the lithiated anion of *t*-BuOAc. The diazo functionality was then successfully introduced to provide 14 in 70% yield over two steps. Subsequent oxidation with PCC delivered the corresponding ketone 15 in 66% yield. Formation of the γ -alkylidenebutenolide 4a through Cu-mediated coupling with (*Z*)-iodoacrylic acid 7a proceeded smoothly (58%). Notably, the diazo function did not undergo any side reaction and was untouched by the copper employed in this transformation, once again demonstrating the versatility of this method.

With cyclisation precursor 4a in hand, we were ready to explore the key intramolecular rhodium(II)-mediated [1,3]-dipolar cycloaddition reaction. In the event, we were pleased to observe the smooth formation of spiro lactone 2c in the presence of a catalytic amount of $\text{Rh}_2(\text{OAc})_4$ in dichloromethane at room temperature, in good yield (78%) and as a single diastereomer (Scheme 10). The reaction is presumed to proceed *via* initial carbonyl ylide formation followed by a chemo-, regio- and diastereoselective intramolecular cycloaddition reaction onto the exocyclic double bond of the dipolarophile. The relative stereochemistry was unambiguously secured through X-ray crystallographic analysis.²¹

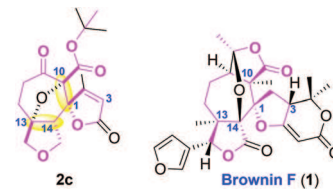


Fig. 4 (5,7,5) tricyclic spiro core of brownin F.

Avoiding the formation of the double bond in the seven-membered ring proved to be most beneficial as polycyclic structure 2c was now much more stable and could be straightforwardly purified by flash chromatography on silica gel. Our strategy represents the first reported synthesis of the (5,7,5) tricyclic spiro core of brownin F. Such an approach allowed us to diastereoselectively install four stereocentres, three of which were tetrasubstituted, with the required relative stereochemistry at C-1, C-10, C-13 and C-14 (Fig. 4).

Conclusion

In summary, we have achieved a concise, stereocontrolled synthesis of the highly strained tricyclic core of brownin F through two distinct strategies: (i) a thermal exposure of acetoxypyranones and (ii) a metal-catalysed decomposition of α -diazoketones. Even though the [3 + 2] cycloaddition proceeded smoothly and efficiently in both cases, the rhodium mediated approach gave a more stable cycloadduct and allowed the creation of an extra tetrasubstituted stereocentre. Research is in progress for further functionalisation towards the synthesis of the pentacyclic core of brownin F.

Experimental section

^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC400 (400 MHz) and a Bruker AC300 (75 MHz) spectrometer respectively. Infra-red spectra were recorded on a Bruker VERTEX70 Fourier transform infrared spectrometer fitted with a single reflection diamond ATR Bruker A222 accessory. High-resolution mass spectra (HRMS) were performed on a QStar Elite (Applied Biosystems SCIEX) spectrometer equipped with atmospheric pressure ionization source (API). Analytical thin layer chromatography (TLC) was carried out on Merck® Kieselgel 60 F254 plates and achieved under a 254 nm UV light, visualized with a KMnO_4 solution.

Flash column chromatography was carried out on Merck® Kieselgel 60 (230–400 mesh) silica gel. Anhydrous THF, dichloromethane, toluene and Et₂O were obtained from a MBraun® SPS-800 solvent purification system. All experiments were performed under anhydrous conditions and an inert atmosphere of argon and, except where stated, using dried apparatus and employing standard techniques for handling air-sensitive materials.

General procedure for the preparation of γ -alkylidenebutenolides

A dry Schlenk tube equipped with a Teflon-coated magnetic stirrer was charged with K₂CO₃ (3 equiv.) and (*Z*)-3-iodobut-2-enoic acid (2 equiv.). The vessel was evacuated and backfilled with argon. Anhydrous DMF (*c* = 1.9 M) was added and the suspension was stirred for 15 min. Then the reaction mixture was degassed at 0 °C for 5 min under *vacuum* and backfilled with argon. After reaching room temperature, the previously prepared alkyne (1 equiv.) and CuI (1 equiv.) were successively added. The Schlenk tube was sealed and then placed in a preheated oil bath at 55 °C for 4 hours, following which the Schlenk tube was placed in an ice bath and a saturated aqueous solution of NH₄Cl was added. Stirring at 0 °C was allowed for 10 min and the reaction mixture was diluted in diethyl ether and filtered through a short pad of celite. The filtrate was washed with brine and the combined organic layers were dried over anhydrous MgSO₄, filtered and concentrated *in vacuo*.

Compound 9. The expected γ -alkylidenebutenolide (1.20 g; 89% yield) was used in the next step without further purification. *R_f* (PE–AcOEt: 9/1) = 0.15; HRMS (ES) *m/z* calcd for C₁₉H₂₈O₅Si + NH₄⁺: 382.2044, [M + NH₄⁺], found 382.2043; ¹H NMR (CDCl₃, 400 MHz): δ (ppm) 0.08 (6H, 2 × CH₃, s), 0.90 (9H, 3 × CH₃, s), 2.13 (3H, CH₃, d, *J* = 1.5 Hz), 4.35 (2H, CH₂, d, *J* = 7.0 Hz), 4.46 (2H, CH₂, s), 4.62 (2H, CH₂, s), 5.4 (1H, CH, t, *J* = 6.3 Hz), 5.97 (1H, CH, br s), 6.18 (1H, CH, d, *J* = 3.3 Hz), 6.29 (1H, CH, d, *J* = 3.3 Hz). ¹³C (CDCl₃, 100 MHz): δ (ppm) –5.3 (2 × CH₃), 11.7 (CH₃), 18.4 (C), 25.9 (3 × CH₃), 58.3 (CH₂), 64.0 (CH₂), 64.7 (CH₂), 107.9 (2 × CH), 110.6 (CH), 117.3 (CH), 150.5 (C), 151.2 (C), 154.6 (C), 155.0 (C), 168.7 (C).

Compound 4a. The resulting crude material was purified by flash chromatography on silica gel (PE–EtOAc: 70/30). Fractions that contained the desired product were gathered and concentrated under reduced pressure to give the γ -alkylidenebutenolide (0.11 g) in 58% yield. *R_f* (PE–EtOAc: 6/4) = 0.29; HRMS (ESI): *m/z* calcd for C₁₈H₂₂N₂O₇ + H⁺: 379.1500, [M + H⁺], found 379.1499; ¹H NMR (benzene-d₆, 400 MHz): δ (ppm) 1.20 (3H, CH₃, d, *J* = 1.32 Hz), 1.25 (9H, CH₃, s), 2.43–2.47 (2H, CH₂, m), 3.11–3.15 (1H, CH₂, m), 3.78 (2H, CH₂, s), 4.13 (1H, CH₂, d, *J* = 6.80 Hz), 4.96 (1H, CH, t, *J* = 6.80 Hz), 5.28 (1H, CH, br s). ¹³C NMR (benzene-d₆, 100 MHz): δ (ppm) 10.8 (CH₃), 28.1 (3 × CH₃), 32.5 (CH₂), 34.5 (CH₂), 65.7 (CH₂), 75.7 (CH₂), 82.4 (C), 106.8 (CH), 117.5 (CH), 150.5 (C), 154.0 (C), 160.5 (C), 167.9 (C), 190.9 (C), 206.0 (C), (C=N₂ was not observed);²² IR: ν_{\max} 2978, 2931, 2133, 1768, 1711, 1649, 1369, 1312, 1134 cm^{–1}.

Compound 6. To a cooled (0 °C) solution of the γ -alkylidenebutenolide **9** (1 equiv.; 1.20 g) in anhydrous THF (*c* = 0.27 M) was added a solution of HF–pyridine (70%/30%) (2 equiv.). Stirring at room temperature was allowed until completion of the reaction by TLC at which time a saturated aqueous solution of NaHCO₃ was carefully added to quench the reaction. The aqueous phase was extracted with Et₂O and the combined organic layers were dried over anhydrous MgSO₄, filtered and concentrated *in vacuo*. The resulting oil was purified by flash chromatography on silica gel (PE–AcOEt: 1/1). Fractions that contained the desired product were gathered and concentrated under reduced pressure to give the alcohol (0.70 g) in 75% yield (over 2 steps) as a yellow solid. Mp = 47.2 °C; *R_f* (PE–AcOEt: 1/1) = 0.17; HRMS (ES) *m/z* calcd for C₁₃H₁₄O₅ + NH₄⁺: 268.1179, [M + NH₄⁺], found 268.1179; ¹H NMR (CDCl₃, 400 MHz): δ (ppm) 2.14 (3H, 3 × CH₃, s), 4.36 (2H, CH₂, dd, *J* = 7.0 Hz), 4.47 (2H, CH₂, s), 4.60 (2H, CH₂, s), 5.40 (1H, CH, t, *J* = 7.0 Hz), 5.98 (1H, CH, s), 6.25 (1H, CH, d, *J* = 3.1 Hz), 6.31 (1H, CH, d, *J* = 3.1 Hz). ¹³C NMR (CDCl₃, 100 MHz): δ (ppm) 11.9 (CH₃), 57.7 (CH₂), 64.1 (CH₂), 64.7 (CH₂), 107.8 (CH), 108.7 (CH), 110.8 (CH), 117.6 (CH), 151.3 (C), 151.7 (C), 154.8 (2C), 168.9 (C).

Compound 10. To a cooled (–78 °C) solution of alcohol **6** (1 equiv.; 0.60 g) in anhydrous CH₂Cl₂ (*c* = 0.13 M) was added *m*-CPBA (1.1 equiv.). The reaction mixture was allowed to warm to room temperature over a period of an hour and was stirred until completion of the reaction by TLC. Then the reaction mixture was diluted with dichloromethane and the organic layer was washed with a saturated aqueous solution of Na₂CO₃, followed by an aqueous solution of Na₂S₂O₃ (10%). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to give the expected γ -pyrone (0.48 g, 68%) which was used in the next step without further purification. *R_f* (PE–AcOEt: 1/1) = 0.32; HRMS (ES) *m/z* calcd for C₁₃H₁₄O₆ + Na⁺: 289.0683, [M + Na⁺], found 289.0683; ¹H NMR (benzene-d₆, 400 MHz): δ (ppm) 1.21 (3H, CH₃, d, *J* = 1.3 Hz), 3.17 (1H, CH₂, d, *J* = 10.0 Hz), 3.24 (1H, CH₂, d, *J* = 10.0 Hz), 4.00 (1H, CH₂, d, *J* = 16.8 Hz), 4.08 (2H, CH₂, m), 4.42 (1H, CH₂, d, *J* = 16.8 Hz), 4.78 (1H, CH, t, *J* = 6.5 Hz), 5.29 (1H, CH, br s), 5.84 (1H, CH, d, *J* = 10.0 Hz), 6.27 (1H, CH, d, *J* = 10.0 Hz). ¹³C NMR (benzene-d₆, 100 MHz): δ (ppm) 11.1 (CH₃), 66.4 (CH₂), 66.9 (CH₂), 75.2 (CH₂), 93.1 (C), 106.4 (CH), 118.0 (CH), 128.1 (CH), 145.8 (CH), 152.0 (C), 154.2 (C), 168.1 (C), 194.0 (C).

Compound 5a. To a cooled (0 °C) solution of the γ -hydroxypyranone **10** (1 equiv.; 0.10 g) in anhydrous CH₂Cl₂ (*c* = 0.07 M) were added freshly distilled pyridine (1.5 equiv.), acetic anhydride (3 equiv.) and DMAP (0.3 equiv.). Stirring at 0 °C was allowed for 30 min and then at room temperature until the disappearance of the starting material by TLC. Thereafter, the reaction mixture was quenched with water and the aqueous phase was extracted three times with CH₂Cl₂. The combined organic layers were washed twice with an aqueous solution of HCl (5%), with a saturated aqueous solution of NaHCO₃ (4 times), and with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The resulting

crude solid was used in the next step without further purification. Mp = 87 °C; R_f (PE-AcOEt: 1/1) = 0.47; HRMS (ES) m/z calcd for $C_{15}H_{16}O_7 + NH_4^+$: 326.1234, $[M + NH_4^+]$, found 326.1234; 1H NMR (benzene- d_6 , 400 MHz): δ (ppm) 1.1 (3H, CH_3 , d, $J = 1.5$ Hz), 1.55 (3H, CH_3 , s), 3.61 (1H, CH, d, $J = 10.5$ Hz), 3.83 (1H, CH, d, $J = 10.5$ Hz), 4.06 (1H, CH, d, $J = 16.8$ Hz), 4.10–4.20 (2H, CH_2 , m), 4.41 (1H, CH, d, $J = 16.1$ Hz), 4.81 (1H, CH, t, $J = 6.6$ Hz), 5.26 (1H, CH, br s), 5.89 (1H, CH, d, $J = 10.5$ Hz), 6.91 (1H, CH, d, $J = 10.5$ Hz). ^{13}C NMR (benzene- d_6 , 100 MHz): δ (ppm) 10.8 (CH_3), 20.8 (CH_3), 66.1 (CH_2), 68.1 (CH_2), 72.9 (CH_2), 98.5 (C), 106.3 (CH), 117.7 (CH), 128.1 (CH), 144.2 (CH), 151.6 (C), 153.9 (C), 167.7 (C), 168.9 (C), 192.6 (C).

Compound 5b. See the procedure used for compound 5a.

The resulting crude orange oil was used in the next step without further purification. R_f (PE-AcOEt: 1/1) = 0.58; 1H NMR (benzene- d_6 , 400 MHz): δ (ppm) 1.21 (3H, CH_3 , s, H_{10}), 1.58 (3H, CH_3 , s, H_{15}), 3.61 (1H, CH, d, $J = 10.5$ Hz, H_{5a}), 3.83 (1H, CH, d, $J = 10.5$ Hz, H_{5b}), 4.04–4.10 (3H, CH_2 and CH_2 , m, H_{6a} and H_7), 4.42 (1H, CH, d, $J = 17.1$ Hz, H_{6b}), 4.85 (1H, CH, t, $J = 6.8$ Hz, H_8), 5.93 (1H, CH, d, $J = 10.5$ Hz, H_2), 6.94 (1H, CH, d, $J = 10.5$ Hz, H_3). ^{13}C NMR (benzene- d_6 , 100 MHz): δ (ppm) 10.7 (CH_3 , C_{10}), 20.8 (CH_3 , C_{15}), 65.7 (CH_2 , C_7), 68.1 (CH_2 , C_6), 73.0 (CH_2 , C_5), 98.5 (C, C_4), 107.7 (CH, C_8), 112.3 (C, C_{12}), 128.1 (CH, C_2), 144.1 (CH, C_3), 149.8 (C, C_9 or C_{11}), 150.4 (C, C_9 or C_{11}), 163.6 (C, C_{13}), 168.9 (C, C_{14}), 192.6 (C, C_{14}).

General procedure for the base promoted [3 + 2] cyclisation

To a stirred solution of the previously prepared acetate 5 (1 equiv.) in freshly distilled MeCN was added freshly distilled NEt_3 (1.1 equiv.). The reaction medium was heated until disappearance of the starting material by TLC (3 hours). The reaction mixture was cooled to room temperature at which time it was quenched with water and diluted with EtOAc. The aqueous layer was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo*. When possible, purification by chromatography on silica gel was carried out.

Cycloadduct 2a. 100% conversion (0.079 g); 1H NMR (acetone- d_6 , 400 MHz): δ (ppm) 1.88 (3H, CH_3 , d, $J = 1.5$ Hz), 3.42 (1H, CH, dd, $J = 8.3$ Hz, $J = 4.02$ Hz), 3.76–3.82 (1H, CH_2 , m), 3.89 (1H, CH_2 , d, $J = 10.5$ Hz), 4.00–4.03 (1H, CH_2 , m), 4.15 (1H, CH_2 , d, $J = 10.5$ Hz), 4.54 (1H, CH, s), 6.00–6.02 (1H, CH, br s), 6.18 (1H, CH, dd, $J = 9.8$ Hz, $J = 1.0$ Hz), 7.83 (1H, CH, d, $J = 9.8$ Hz).

Cycloadduct 2b. 55% yield (0.055 g); white crystal; Mp = 196.5 °C; 1H NMR (acetone- d_6 , 400 MHz): δ (ppm) 1.85 (3H, CH_3 , s), 3.47 (1H, CH, dd, $J = 3.8$ Hz, $J = 8.5$ Hz), 3.78–3.83 (1H, CH, m), 3.90 (1H, CH, d, $J = 10.7$ Hz), 4.04 (1H, CH, dd, $J = 9.8$ Hz, $J = 3.8$ Hz), 4.18 (1H, CH, d, $J = 10.7$ Hz), 4.67 (1H, CH, s), 6.23 (1H, CH, dd, $J = 9.8$ Hz, $J = 1.0$ Hz), 7.87 (1H, CH, d, $J = 9.8$ Hz); ^{13}C NMR (acetone- d_6 , 100 MHz): δ (ppm) 14.4 (CH_3), 57.4 (CH), 67.6 (CH_2), 73.7 (CH_2), 94.2 (CH), 94.5 (C), 95.8 (C), 112.4 (C), 128.5 (CH), 154.7 (CH), 160.5 (C), 166.7 (C), 193.7 (C).

Compound 11. To a cooled (0 °C) solution of cycloadduct 2a (0.090 g, 0.364 mmol, 1 equiv.) in anhydrous MeOH (8 mL) was added $CeCl_3 \cdot 7H_2O$ (0.149 g, 0.401 mmol, 1.1 equiv.). Stirring was allowed for 10 min before the portionwise addition of $NaBH_4$ (0.015 g, 0.401 mmol, 1.1 equiv.). Stirring at room temperature was allowed for one hour and H_2O was added. The aqueous phase was extracted with CH_2Cl_2 (4 times) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo*. The resulting oil was purified by flash chromatography on florisil (PE-EtOAc: 1/1). Fractions that contained the desired product were gathered and concentrated under reduced pressure to afford 20.1 mg of the desired product 11 (15% yield) as a white solid. HRMS (ES) m/z calcd for $C_{13}H_{14}O_5 + NH_4^+$: 268.1179, $[M + NH_4^+]$, found 268.1181. 1H NMR (acetone- d_6 , 400 MHz): δ (ppm) 1.53 (3H, CH_3 , s, H_2), 2.70 (1H, CH, d, $J = 19.0$ Hz), 2.94 (1H, CH, d, $J = 19.0$ Hz), 3.25 (1H, CH, t, $J = 9.0$ Hz), 3.91–3.95 (3H, CH_2 and CH_2 , m), 4.0 (1H, CH, d, $J = 10.3$ Hz), 4.65 (1H, CH, dd, $J = 3.8$ Hz, $J = 6.8$ Hz), 4.98 (1H, CH, d, $J = 6.8$ Hz), 5.86 (1H, CH, ddd, $J = 3.8$ Hz, $J = 9.5$ Hz, $J = 0.8$ Hz), 6.44 (1H, CH, d, $J = 9.5$ Hz). ^{13}C NMR (acetone- d_6 , 100 MHz): δ (ppm) 25.9 (CH_3), 46.1 (CH_2), 56.0 (CH), 68.9 (CH_2), 72.1 (CH), 74.6 (CH_2), 84.9 (C), 89.5 (CH), 92.7 (C), 100.6 (C), 129.7 (CH), 153.9 (CH), 173.8 (C).

Compound 12. To a stirred solution of alcohol 13 (2 g, 17.2 mmol, 1 equiv.) in anhydrous DMF (13 mL) and THF (19 mL) were added NaH (60% dispersion in mineral oil, 0.62 g, 26 mmol, 1.5 equiv.) and propargyl bromide (80% w/w, 7.3 g, 34.4 mmol, 1.4 equiv.). Stirring at room temperature was allowed for 7 hours at which time a saturated aqueous solution of NH_4Cl was poured into the reaction mixture. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo*. The resulting oil was purified by flash chromatography on silica gel (PE-EtOAc: 7/3). Fractions that contained the desired product 12 were gathered, and concentrated under reduced pressure (38% yield, 1.0 g). R_f (PE-Et $_2$ O: 7/3) = 0.2; HRMS (ESI): m/z calcd for $C_8H_{10}O_3 + H^+$: 155.0703, $[M + H^+]$, found 155.0702; 1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.09–2.05 (1H, CH_2 , m, H_{3a}), 2.26–2.35 (1H, CH_2 , m, H_{3b}), 2.44–2.52 (2H, CH and CH_2 , m, H_8 and H_{2a}), 2.56–2.65 (1H, CH_2 , m, H_{2b}), 3.71 (2H, CH_2 , ddd, $J = 3.5$ Hz, $J = 4.3$ Hz, $J = 10.6$ Hz, H_5), 4.20 (2H, CH_2 , ddd, $J = 2.3$ Hz, $J = 2.5$ Hz, $J = 15.8$ Hz, H_6), 4.64–4.69 (2H, CH_2 , m, H_4). ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 24.0 (CH_2 , C_3), 28.3 (CH_2 , C_2), 58.7 (CH_2 , C_6), 71.1 (CH_2 , C_5), 75.0 (CH, C_8), 78.6 (CH, C_4), 79.0 (C, C_7), 177.1 (C, C_1). IR: ν_{max} 3275, 2942, 2864, 2117, 1765, 1460, 1421, 1354, 1183, 1166, 1111, 1056, 1010, 943 cm^{-1} .

Compound 14. To a cooled (–78 °C) stirred solution of diisopropylamine (0.98 g, 9.7 mmol, 1.2 equiv.) in anhydrous THF (24 mL) was added dropwise *n*-BuLi (4.1 mL, 2.4 M solution in hexane, 9.7 mmol, 1.2 equiv.). After 45 min at this temperature, a solution of *t*-BuOAc (1.13 g, 9.7 mmol, 1.2 equiv.) in anhydrous THF (43 mL) was added dropwise to the reaction mixture. After an additional 45 min at –78 °C, a solution of the previously prepared lactone 12 (1.25 g,

8.11 mmol, 1 equiv.) in anhydrous THF (13 mL) was added. The reaction mixture was stirred at this temperature for 2 hours at which time it was rapidly transferred to a saturated aqueous solution of NH_4Cl . Then the aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo* to afford a clear yellow oil which was used in the next step without further purification.

To a cooled (0 °C) stirred solution of the crude β -ketoester (2.2 g, 8.15 mmol, 1 equiv.) in anhydrous acetonitrile (130 mL) were added successively triethylamine (1.15 g, 11.4 mmol, 1.4 equiv., 1.6 mL) and *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (2.15 g, 8.97 mmol, 1.1 equiv.). The reaction mixture was stirred at 25 °C for 14 hours at which time it was filtered. Then the filtrate was concentrated under reduced pressure and the resulting solid was triturated in CH_2Cl_2 and filtered again. The filtrate was concentrated *in vacuo* and the crude oil was next purified by flash chromatography on silica gel (PE–EtOAc: 80/20) and furnished 1.7 g of the diazo compound **14** (70% yield over 2 steps). R_f (PE–EtOAc: 8/2) = 0.12; HRMS (ESI): m/z calcd for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_5 + \text{Na}^+$: 319.1264, $[\text{M} + \text{Na}^+]$, found 319.1263; ^1H NMR (benzene- d_6 , 400 MHz): δ (ppm) 1.25 (9H, CH_3 , s), 1.75–1.86 (2H, CH_2 , m), 2.01 (1H, CH, t, $J = 2.5$ Hz), 2.33 (1H, OH, m), 2.98 (2H, CH_2 , td, $J = 7.3$ Hz, $J = 2.0$ Hz), 3.19–3.23 (1H, CH_2 , m), 3.27–3.30 (1H, CH_2 , m), 3.71–3.77 (3H, CH and CH_2 , m). ^{13}C NMR (benzene- d_6 , 100 MHz): δ (ppm) 28.0 (CH_2), 28.1 ($3 \times \text{CH}_3$), 36.8 (CH_2), 58.4 (CH_2), 69.8 (CH), 74.5 (CH_2), 74.7 (CH), 80.1 (C), 82.3 (C), 160.6 (C), 192.4 (C), (C=N2 was not observed);²² IR: ν_{max} 3482, 3273, 2937, 1767, 1351, 1186, 1113, 1054, 1009, 940 cm^{-1} .

Compound 15. To a stirred solution of diazo compound **14** (0.7 g, 2.27 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (22 mL) were added NaOAc (0.028 g, 0.34 mmol, 0.15 equiv.) and PCC (0.59 g, 2.73 mmol, 1 equiv.). Stirring at 25 °C was allowed for 24 hours at which time the reaction mixture was filtered through a pad of celite. Then the filtrate was concentrated *in vacuo* to yield a yellow oil which was purified by flash chromatography on silica gel (PE–EtOAc: 9/1) and furnished 0.438 g of ketone **15** (66% yield). R_f (PE–EtOAc: 8/2) = 0.26; HRMS (ESI): m/z calcd for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_5 + \text{H}^+$: 295.1288, $[\text{M} + \text{H}^+]$, found 295.1289; ^1H NMR (benzene- d_6 , 400 MHz): δ (ppm) 1.25 (9H, CH_3 , s), 1.99 (1H, CH_2 , t, $J = 2.3$ Hz), 2.46–2.49 (2H, CH_2 , m), 3.06–3.09 (2H, CH_2 , m), 3.87 (2H, CH_2 , s), 3.87 (2H, CH_2 , d, $J = 2.3$ Hz). ^{13}C NMR (benzene- d_6 , 100 MHz): δ (ppm) 28.1 ($3 \times \text{CH}_3$), 32.6 (CH_2), 34.3 (CH_2), 58.3 (CH_2), 74.4 (CH_2), 75.3 (CH), 79.4 (C), 82.3 (C), 160.5 (C), 190.8 (C, C_8), 206.1 (C, C_5), (C=N2 was not observed);²² IR: ν_{max} 3273, 2981, 2133, 1731, 1711, 1649, 1370, 1313, 1258, 1228, 1132, 1106, 1026 cm^{-1} .

Cycloadduct 2c. To a stirred solution of diazo compound **4a** (0.098 g, 0.26 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (1.5 mL, $c = 0.16$ M) was added in one portion $\text{Rh}_2(\text{OAc})_4$ (5.7 mg, 0.013 mmol, 0.05 equiv.). Stirring at room temperature was allowed for 2 hours at which time the mixture was concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel (PE–EtOAc: 40/60).

Fractions that contained the desired product **2c** were gathered and concentrated under reduced pressure to give the cycloadduct in 78% yield as a white solid (0.071 g). R_f (PE–EtOAc: 4/6) = 0.1; HRMS (ESI): m/z calcd for $\text{C}_{18}\text{H}_{22}\text{O}_7 + \text{NH}_4^+$: 368.1703, $[\text{M} + \text{NH}_4^+]$, found 368.1704; ^1H NMR (CDCl_3 , 400 MHz): δ (ppm) 1.44 (9H, $3 \times \text{CH}_3$, s), 1.20 (3H, CH_3 , d, $J = 1.5$ Hz), 2.06–2.12 (1H, CH_2 , m), 2.54–2.72 (2H, $2 \times \text{CH}_2$, m), 2.89–2.97 (1H, CH_2 , m), 3.03 (1H, CH, dd, $J = 1.8$ Hz, $J = 7.3$ Hz), 3.51 (1H, CH_2 , d, $J = 10.5$ Hz), 3.66 (1H, CH_2 , dd, $J = 7.3$ Hz, $J = 10.0$ Hz), 3.98 (1H, CH_2 , dd, $J = 1.8$ Hz, $J = 10.0$ Hz), 4.37 (1H, CH_2 , d, $J = 10.5$ Hz), 5.95 (1H, CH, q, $J = 1.5$ Hz). ^{13}C NMR (CDCl_3 , 100 MHz): δ (ppm) 14.0 (CH_3), 27.6 ($3 \times \text{CH}_3$), 28.4 (CH_2), 35.6 (CH_2), 54.9 (CH), 67.0 (CH_2), 74.7 (CH_2), 84.4 (C), 91.7 (C), 95.8 (C), 96.6 (C), 120.8 (CH, C_{11}), 161.1 (C, C_{10}), 163.7 (C, C_{14}), 170.1 (C, C_{12}), 200.0 (C, C_1). IR: ν_{max} 2991, 2973, 2939, 2909, 2867, 1755, 1721, 1638, 1455, 1370, 1305, 1225, 1152, 1101, 953 cm^{-1} .

Acknowledgements

The Agence Nationale pour la Recherche (A.N.R.-09-JCJC-0036), the CNRS and Aix Marseille Université (UMR 7313) are gratefully acknowledged for financial support. The authors wish to thank Michel Giorgi for X-ray analysis.

Notes and references

- (a) K. Koike, K. Mitsunaga, K. Ishii, T. Ohmoto, Y. Kawakami, M. Ikemori and T. Sato, *Tetrahedron*, 1993, **49**, 2209; (b) K. Mitsunaga, K. Koike, K. Ishii, T. Ohmoto, A. Uchida, I. Oonishi and Y. Ohashi, *Tetrahedron Lett.*, 1993, **34**, 6415; (c) K. Mitsunaga, K. Koike, K. Ishii and T. Ohmoto, *Phytochemistry*, 1994, **35**, 451; (d) K. Mitsunaga, K. Koike, K. Ishii and T. Ohmoto, *Phytochemistry*, 1994, **37**, 1443.
- F. Rodier, M. Rajzmann, J.-L. Parrain, G. Chouraqui and L. Commeiras, *Chem.-Eur. J.*, 2013, **19**, 2467.
- (a) R. Blanc, V. Héran, R. Rahmani, L. Commeiras and J.-L. Parrain, *Org. Biomol. Chem.*, 2010, **8**, 5490; (b) S. Dubois, F. Rodier, R. Blanc, R. Rahmani, J. Thibonnet, V. Héran, L. Commeiras and J.-L. Parrain, *Org. Biomol. Chem.*, 2012, **10**, 4712.
- A. Bartoli, G. Chouraqui and J.-L. Parrain, *Org. Lett.*, 2012, **14**, 122.
- For books and reviews on 1,3-dipolar cycloadditions of carbonyl ylides, see: (a) A. Padwa and M. D. Weingarten, *Chem. Rev.*, 1996, **96**, 223; (b) M. P. Doyle, M. A. McKervey and T. Ye, in *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley-Interscience, New York, 1998, ch. 7; (c) D. M. Hodgson, F. Y. T. M. Pierard and P. A. Stuppel, *Chem. Soc. Rev.*, 2001, **30**, 50; (d) G. Mehta and S. Muthusamy, *Tetrahedron*, 2002, **58**, 9477; (e) R. M. Savizky and D. J. Austin, in *Modern Rhodium-Catalyzed Organic Reactions*, ed. P. A. Evans, Wiley-VCH,

- Weinheim, 2005, ch. 19; (f) M. C. McMills and D. Wright, in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, ed. A. Padwa and W. H. Pearson, John Wiley & Sons, Hoboken, 2003, ch. 4; (g) V. Nair and T. D. Suja, *Tetrahedron*, 2007, **63**, 12247; (h) V. Singh, U. M. Krishna, Vikrant and G. K. Trivedi, *Tetrahedron*, 2008, **64**, 3405; (i) A. Padwa, *Chem. Soc. Rev.*, 2009, **38**, 3072.
- 6 (a) M. P. Doyle, *Acc. Chem. Res.*, 1986, **19**, 348; (b) G. Maas, *Top. Curr. Chem.*, 1987, **137**, 75; (c) K. H. Dötz, *Angew. Chem., Int. Ed.*, 1975, **14**, 644; (d) W. D. Wulff, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, New York, 1990, vol. 5; (e) D. S. Wulfman, G. Linstrumelle and C. F. Cooper, in *The Chemistry of Diazonium and Diazo Groups*, ed. S. Patai, Wiley Interscience, New York, 1978, Part 2, ch. 18.
- 7 J. B. Hendrickson and J. S. Farina, *J. Org. Chem.*, 1980, **45**, 3359.
- 8 O. Achmatowicz, P. Bukowski, B. Szechner, Z. Zwierzchowska and A. Zamojski, *Tetrahedron*, 1971, **27**, 1973.
- 9 S. Inack-Ngi, R. Rahmani, L. Commeiras, G. Chouraqui, J. Thibonnet, A. Duchêne, M. Abarbri and J.-L. Parrain, *Adv. Synth. Catal.*, 2009, **351**, 779.
- 10 M. Abarbri, J.-L. Parrain and A. Duchêne, *Tetrahedron*, 1995, **36**, 2469.
- 11 S. Celanire, F. Marlin, J. E. Baldwin and R. M. Adlington, *Tetrahedron*, 2005, **61**, 3025.
- 12 S. C. Wang and D. J. Tantillo, *J. Org. Chem.*, 2008, **60**, 833.
- 13 (a) J. C. Slater, *Phys. Rev.*, 1951, **81**, 385; (b) S. H. Vosko, L. Wilk and M. Nussair, *Can. J. Phys.*, 1980, **58**, 1200; (c) A. D. Becke, *Phys. Rev. A*, 1988, **38**, 3098; (d) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B: Condens. Matter*, 1988, **37**, 785; (e) A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.
- 14 D. R. Williams, J. W. Benbow, J. G. McNutt and E. E. Allen, *J. Org. Chem.*, 1995, **60**, 833.
- 15 (a) J. L. Luche, *J. Am. Chem. Soc.*, 1978, **100**, 2226; (b) A. L. Gemal and J. L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454.
- 16 CCDC 906866 contains the supplementary crystallographic data for this paper.
- 17 All details about the formation of such molecules are given in the ESI.†
- 18 S. Inack-Ngi, C. Khalil, V. Héran, L. Commeiras, J.-L. Parrain, A. Duchêne, M. Abarbri and J. Thibonnet, *Chem.–Eur. J.*, 2011, **17**, 13692.
- 19 See ESI.†
- 20 I. E. Wrona, A. E. Gabarda, G. Evano and J. S. Panek, *J. Am. Chem. Soc.*, 2005, **127**, 15026.
- 21 CCDC 907998 contains the supplementary crystallographic data for this paper.
- 22 This is consistent with data previously reported, see for example: (a) H. M. L. Davies, T. Hansen and M. R. Churchill, *J. Am. Chem. Soc.*, 2000, **122**, 3063; (b) F. A. Davis, B. Yang and J. Deng, *J. Org. Chem.*, 2003, **68**, 5147; (c) S. Peddibhotla, Y. Dang, J. O. Liu and D. Romo, *J. Am. Chem. Soc.*, 2007, **129**, 12222.