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Regioselectivity of dimerisation of butenolides via captodative stabilised radicaloid intermediates

Sharanjeet K. Bagal, Robert M. Adlington,† Rohan A. B. Brown and Jack E. Baldwin*

Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK

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Abstract—The regioselective outcome observed during dimerisation of butenolides to dimeric structures via captodative stabilised radicaloids has been studied. The captodative stabilised radicaloids were generated by initial conversion of butenolides to chlorobutenolides via the corresponding hydroxybutenolides, followed by treatment with $CoCl(PPh_3)_3$.

Butenolides, hydroxybutenolides and their corresponding dimers are ubiquitous in nature and possess interesting biological properties. (+)-Atractylolide **1**,[1] (+)-lindestrenolide **2**,[2] lindenanolide H **3**,[3] (+)-hydroxyatractylolide **4**,[1] (+)-hydroxylindestrenolide **5**,[2] strychnistenolide **6**,[3] (+)-styxlactone **7**,[4] (+)-biatractylolide **8**,[5] biepiasterolide **9**,[6] (+)-bilindestenolide **10**[7] and (−)-lindenanolide F **11**[3] are representative members of such compounds that have been isolated from plant sources (Fig. 1).

During our studies on the total synthesis of (±)-biatractylolide **8** and (±)-biepiasterolide **9**,[8–10] a novel general method for the dimerisation of butenolides to dimeric structures via captodative stabilised radicaloids was developed. Our approach involved initial conversion of butenolides to the corresponding hydroxybutenolides, followed by chlorination and treatment with $CoCl(PPh_3)_3$. Thus, five butenolides **1**, **12**–**15** were prepared. Atractylolide **1** and butenolide **12** were prepared as described previously.[8–10] Butenolide **13** was

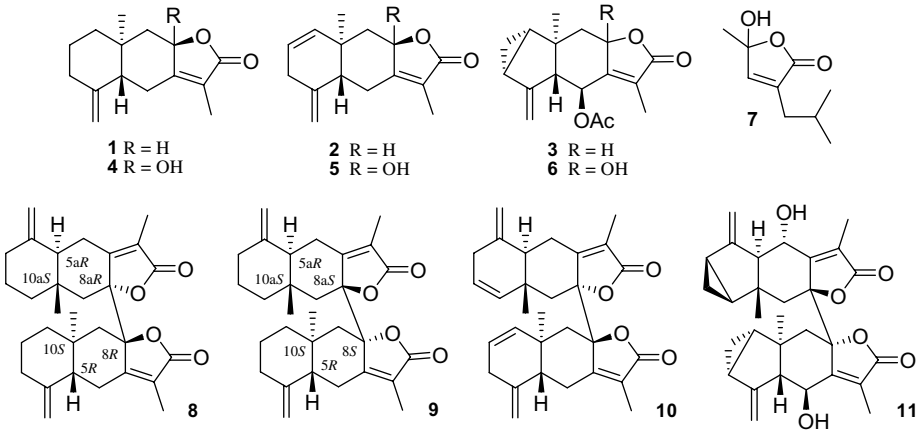

Figure 1. Naturally occurring butenolides, hydroxybutenolides and dimeric butenolides.

Keywords: Dimerisation; Butenolides; Captodative radicaloid.
* Corresponding author. Tel.: +44 (0)1865 275 671; fax: +44 (0)1865 275 632; e-mail addresses: sharanjeet.bagal@magdalen.oxford.ac.uk; robert.adlington@chem.ox.ac.uk
† Tel.: +44 (0)1865 275 626.

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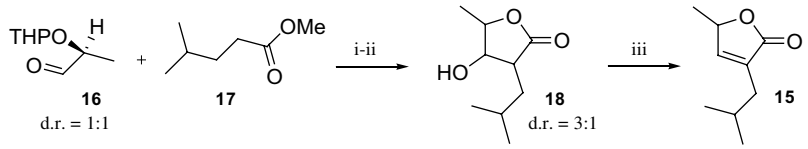
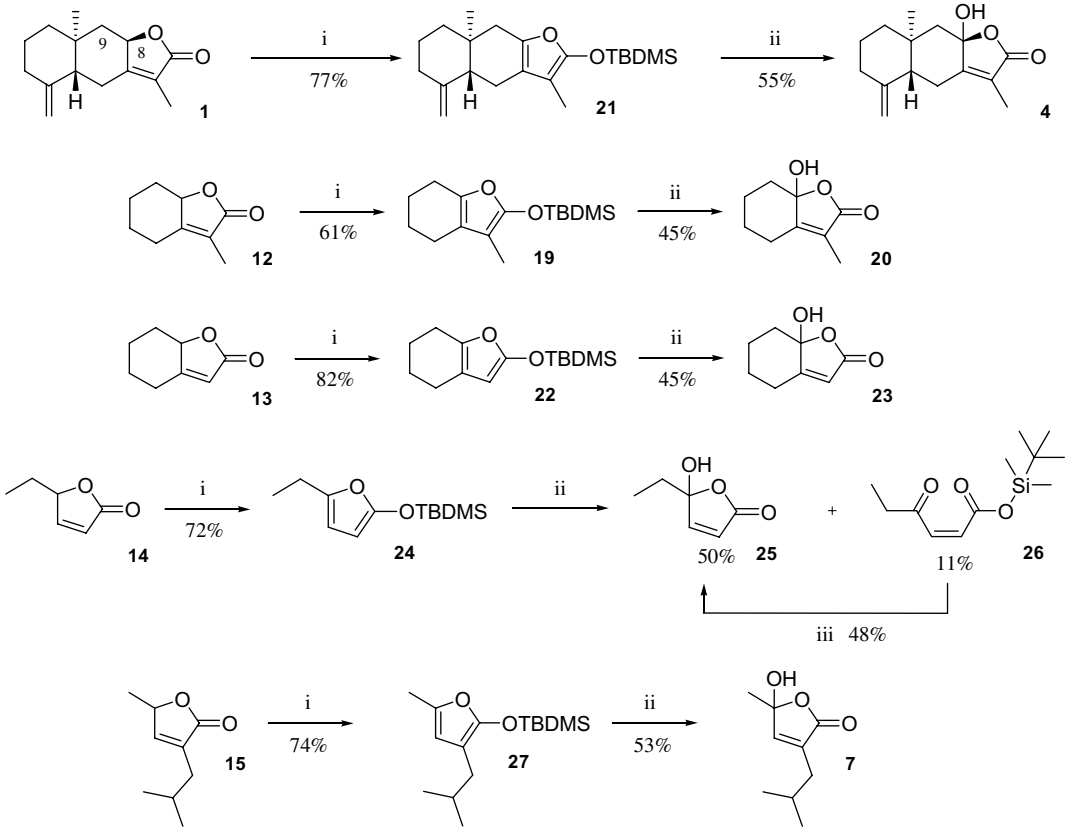


Scheme 1. Reagents and conditions: (i) LDA, HMPA, TMSCl, THF, −78 °C, 1.5 h; (ii) 10% aq HCl–THF (1:3 v/v), rt, 0.5 h, 65% (over two steps); (iii) trifluoroacetic anhydride, TEA, DCM, 0 °C, 10 h, then rt, 2 h, 64%.



Scheme 2. Reagents and conditions: (i) TEA (1.4 equiv), TBDMSOTf (1.3 equiv), DCM, 30 °C, 18 h; (ii) *m*CPBA (1 equiv), DCM, rt, 30 min; (iii) THF–dilute aq HCl (1:1 v/v), rt, 10 min.

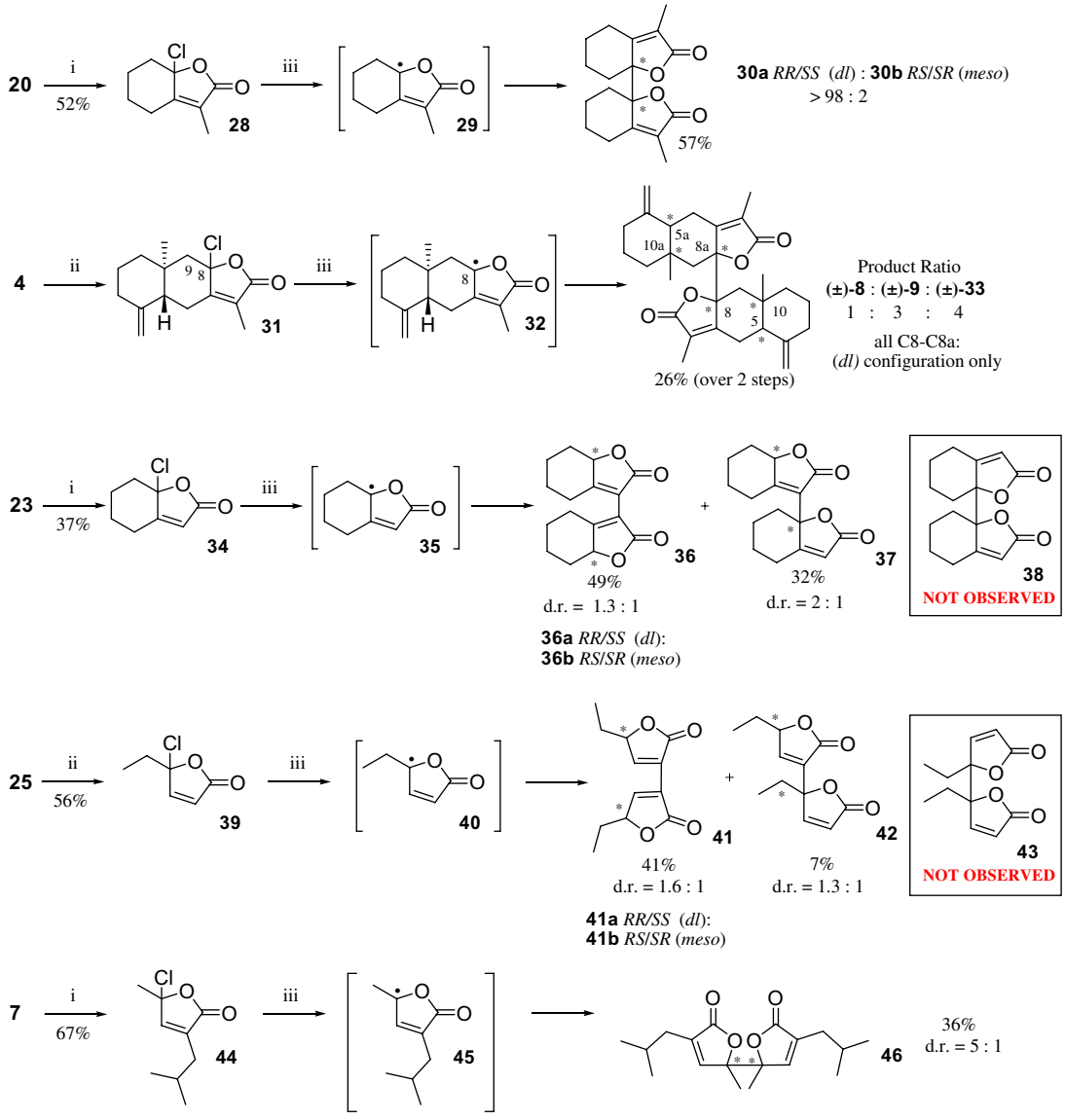
synthesised through the method applied for the synthesis of **12**,[8] whilst butenolide **14** was generated through iodine(III) mediated cyclisation of *trans*-3-hexenoic acid.[11] The styxlactone precursor, butenolide **15**, was obtained by an initial aldol condensation between aldehyde **16**[12] and methyl ester **17**[13] followed by acid catalysed deprotection and lactonisation to afford hydroxylactone **18**, and subsequent trifluoroacetic anhydride mediated dehydration (Scheme 1).

Butenolides **1**, **12**–**15** were transformed into the corresponding hydroxybutenolides **4**, **20**, **23**, **25** and **7**, respectively, in unoptimised yields, by initial conversion to silyloxyfurans **21**, **19**, **22**, **24** and **27**, respectively, followed by *m*CPBA mediated oxidation (Scheme 2).[‡] The mechanism for the oxidation step is believed to proceed via a silylester intermediate,[10] as evidenced by the isolation of silylester **26** during the oxidation of silyloxyfuran **24** and the subsequent facile hydrolysis of **26** with dilute aqueous acid to hydroxybutenolide **25**.

Chlorination with thionyl chloride (in some cases in the presence of pyridine)[8–10] provided the corresponding chlorobutenolides. The side product of halogenation was the 8,9- (or equivalent numbering) dehydration product, which was most likely formed through an E1 mechanism.[9,10] The chlorobutenolides generated **28**, **31**, **34**, **39** and **44** were then treated with freshly prepared $CoCl(PPh_3)_3$,[14] which afforded dimerisation adducts **30**, **8**, **9**, **33**,[§] **36**, **37**, **41**, **42** and **46**, respectively, through the corresponding captodative stabilised[15] radicals **29**, **32**, **35**, **40** and **45**, respectively (Scheme 3).

[‡] Increasing the reaction scale from 1.5 g to 8.0 g of silyloxyfuran **24** during the oxidation of **24** with *m*CPBA improved the isolated yield of **25** to 93%.

[§] Dimer (±)-**33** was shown to be a diastereoisomer of (±)-**8** and (±)-**9** with relative configurations 5*R**, 10*S**, 8*R**–8a*R**, 10a*R**, 5a*S**, through NMR and HRMS analysis and X-ray spectroscopy.[10]



Scheme 3. Yields quoted for the dimerisation of chlorolactone **31** are based upon recovered hydroxyatractylolide **4**. Reagents and conditions: (i) $SOCl_2$, DCM, rt, 18 h; (ii) $SOCl_2$, pyridine, THF, −78 °C, 30 min; (iii) $CoCl(PPh_3)_3$ (1.2 equiv), benzene, rt, 2 h.

The structures of the dimeric products were assigned by HRMS and NMR analysis, and in some cases (**30a**, **8**, **9**, **33**, **36a**, **41a**,**b** and **46**), the three-dimensional structure was unambiguously confirmed by X-ray crystallography (Figs. 2–5).[8–10,16]

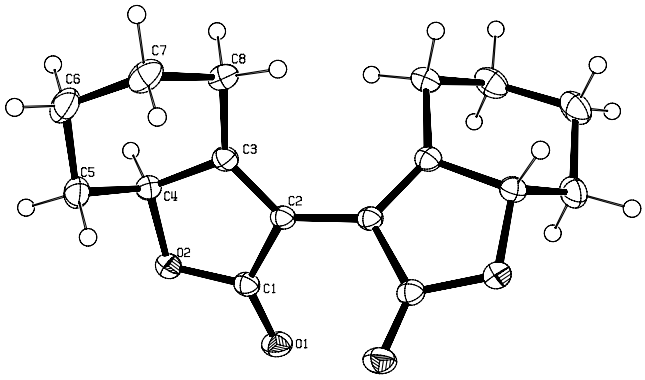


Figure 2. X-ray crystal structure of (±)-**36a**.

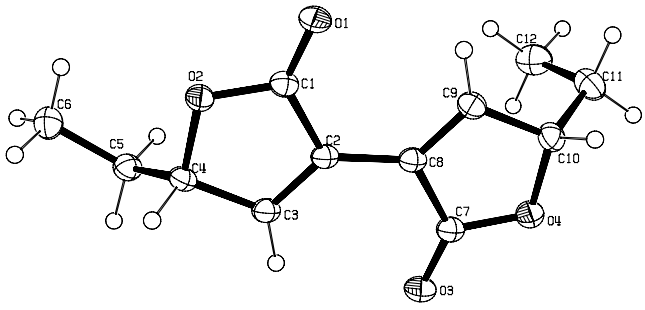


Figure 3. X-ray crystal structure of (±)-**41a**.

It was apparent that the regioselectivity of the cobalt(I) mediated dimerisation was determined by the substituent adjacent to the carbonyl moiety (Cγ) of the chlorolactone precursor (Fig. 6). If the 'Cγ' position was substituted with an alkyl group, as for **28**, **31** and **44**, dimeric adducts derived from 'Cα–Cα′' radical coupling

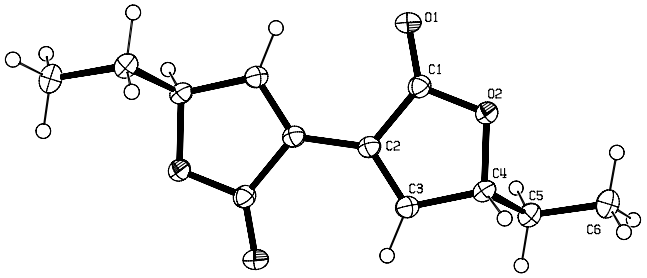


Figure 4. X-ray crystal structure of (±)-**41b**.

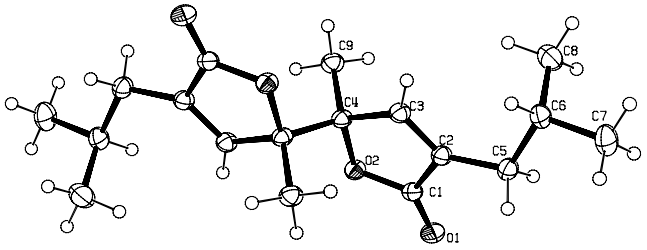


Figure 5. X-ray crystal structure of (±)-*meso* **46**.

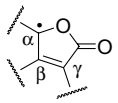


Figure 6.

were isolated, that is, **30**, and biatractylolide **8**, biepiasterolide **9**, **33** and **46**, respectively. However, if hydrogen was appended at the 'Cγ' site, as in the case of chlorobutenolides **34** and **39**, products generated by dimerisation of radicals via the 'Cγ' position were obtained, that is, **36**, **37** and incrustoporin analogue **41**,[17] and **42**, respectively. In these cases, no 'Cα–Cα′' linked adducts, **38** and **43**, respectively, were isolated from the product mixture.

Mechanistically, the formation of the 'Cγ–Cγ′' dimer **36** could most simply be explained by a faster rate of coupling between the less hindered 'Cγ' centres followed by tautomerisation. A similar explanation is given for the formation of dimer **41**. 'Cα–Cγ′' coupled products, that is, **37** and **42**, probably arise again by the result of steric factors on the rate of formation of the C–C bond. By this method the dimerisation of chlorolactones to bisbutenolides with $CoCl(PPh_3)_3$ can be performed with some degree of regiocontrol: the 'Cγ' position should be functionalised with methyl or alkyl substituents if the 'Cα–Cα′' dimer product is required (e.g., **30**, **8**, **9**, **33** and **46**); however, if the 'Cγ' derived dimer products are desired, only hydrogen should be appended at 'Cγ' (e.g., **36**, **37**, **41** and **42**). It should be noted that the formation of dimers **36** and **41** could also be postulated to be derived from intermediate forms of **38** and **43**, respectively, via a [3,3] sigmatropic shift,[18] possibly catalysed by cobalt ion complexation.[19] However, analogous pericyclic proposals seem unlikely as explanations for the formation of dimers **37** and **42** (formally a [1,3] sigmatropic shift from **38** and **43**, respectively). Moreover, our studies have shown that the 'Cγ' derived dimers are stable at room temperature in benzene for 24 h. Instead, therefore, we favour products **36**, **37**, **41** and **42** formation via radicaloid dimerisation from either the 'Cα' or 'Cγ' positions of **35** and **40**, in which individual product forming pathways are subject to steric considerations and under kinetic control.

Conclusion: A general method for the preparation of bisbutenolides from butenolides via the dimerisation of captodative stabilised radicaloids generated using $CoCl(PPh_3)_3$ has been developed. The regioselectivity of the dimerisation process can be controlled to some extent by the substituent appended adjacent to the carbonyl moiety (Cγ) of the chlorolactone precursor.

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