DOI: 10.1002/chem.201101082

Synthesis of the Anti-HIV Agent (−)-Hyperolactone C by Using Oxonium Ylide Formation–Rearrangement

David M. Hodgson* and Stanislav Man[a]

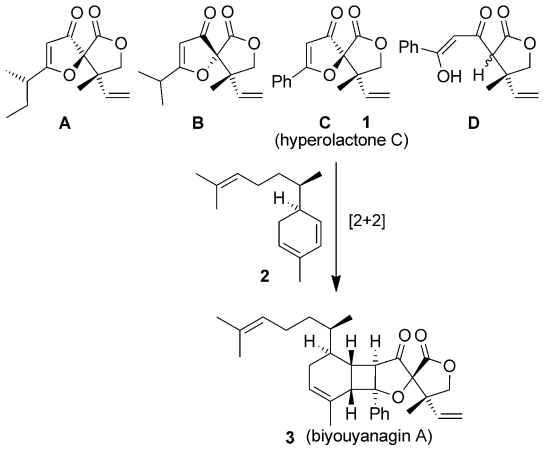
Abstract: Starting from readily available (*S*)-styrene oxide an asymmetric synthesis is described of the naturally occurring anti-HIV spirolactone (−)-hyperolactone C, which possesses adjacent fully substituted stereocenters. The key step involves a stereocontrolled Rh^{II}-catalysed oxonium ylide formation–[2,3] sigmatropic rearrangement of an α-diazo-β-ketoester bearing allylic ether functionality. From the resulting furanone, an acid-catalysed lactonisation and dehydrogenation gives the natural product.

Keywords: hyperolactone · oxonium ylide · rhodium catalysis · sigmatropic rearrangement · total synthesis

Introduction

Hyperolactone C (**1**) is a structurally interesting spirolactone with adjacent quaternary stereocentres and forms part of a small family of related lactones, hyperolactones A–D (Scheme 1) originally isolated from the leaves and stems of *Hypericum chinese* L.[1] First reported in 1995, hyperolactone C has attracted increasing interest following the disclosure in 2005 of a new anti-HIV agent, biyouyanagin A (**3**), which was postulated to be biosynthetically derived by a [2+2] cycloaddition from hyperolactone C and *ent*-zingiberene (**2**).[2] While a subsequent biomimetic synthesis of biyouyanagin A by Nicolaou and co-workers led to correction of the originally proposed stereochemistry of biyouyanagin A to that shown in Scheme 1, the synthesis did support the original biosynthetic hypothesis.[3] More significant in the current context was the finding in follow-on structure–activity studies that the biological activity of biyouyanagin A resides in the hyperolactone C structural domain.[3b] The structural complexity of hyperolactone C and potential as a new lead in anti-HIV research combine to make it an attractive target for synthetic studies.

Four of the five syntheses of hyperolactone C so far reported are summarised in Scheme 2. The first synthesis by Kinoshita in 2001, gave (−)-**1** in 12 steps from malic acid (**4**), and also unambiguously established the absolute configuration of the natural product.[4] However, introduction of the second quaternary stereocentre by reaction of the enolate of lactone **6** with aldehyde **7** proceeded in favour of the undesired diastereomer (40:60 d.r.). In 2004, Kraus and Wei



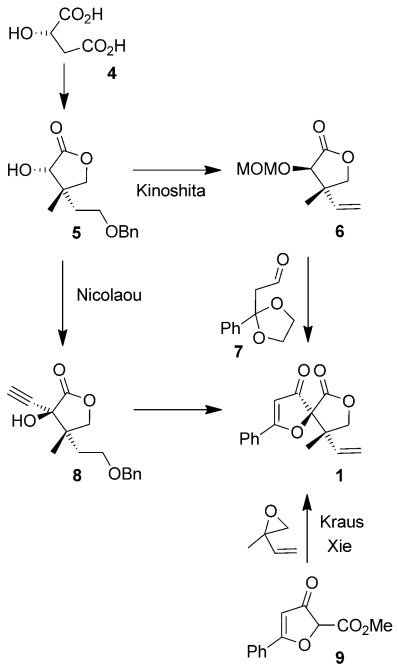
Scheme 1. Hyperolactones A–D and hyperolactone C (**1**) as precursor to biyouyanagin A (**3**).

reported a five-step synthesis of *rac*-**1** from methyl acetoacetate, which involved O-allylation of furanone **9** followed by tandem Claisen rearrangement and lactonisation.[5] This is an elegantly concise synthesis, in which the vicinal stereocentres are created with stereocontrol through a chair-like transition state in the pericyclic step. But the transformation of furanone **9** into *rac*-**1** unfortunately proceeds in only 11% yield, partly due to competing C-allylation. Nicolaou's synthesis of (−)-**1**, on the route to biyouyanagin A (**3**), used a hydroxylactone intermediate **5** from Kinoshita's earlier synthesis and required 11 steps from malic acid (**4**).[3] An improved solution to introduction of the second quaternary stereocentre was achieved by acetylide addition to the ketolactone obtained by oxidation of **5**, which gave alcohol **8** (75:25 d.r.). Alcohol **8** was used in an impressive key-step Pd-catalysed cascade sequence to give the full skeleton of the natural product. Most recently, Xie and co-workers reported in 2009 a six-step catalytic asymmetric synthesis of (−)-**1**.[6] While involving the same disconnection and starting materials as Kraus and Wei, in this case desired C-allylation

[a] Prof. D. M. Hodgson, Dr. S. Man
Department of Chemistry, Chemistry Research Laboratory
University of Oxford, Mansfield Road, Oxford, OX1 3TA (UK)
Fax: (+44) 1865-285002
E-mail: david.hodgson@chem.ox.ac.uk

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201101082.

of furanone **9** under Pd catalysis proceeded in high d.r. (96:4) and excellent e.r. (99.5:0.5), although allylic regioselectivity in the coupling was modest (70:30).



Scheme 2. Overview of previous syntheses to hyperolactone C (**1**).

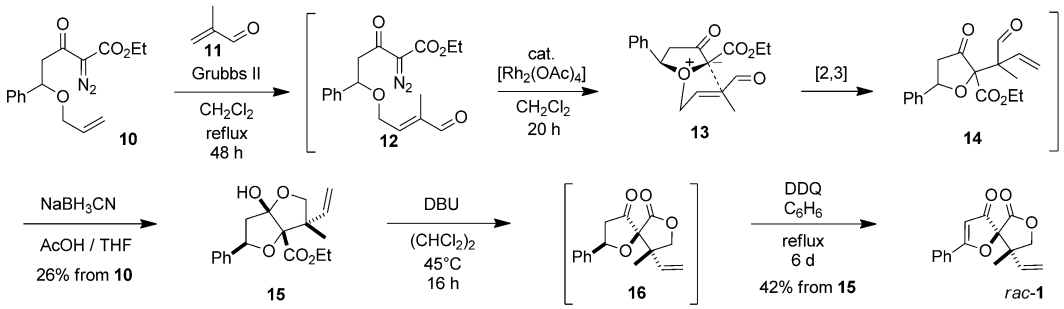
Reported in 2008, our seven-step approach to *rac*-hyperolactone C (**1**) from ethyl acetoacetate involved one-pot *E*-selective cross-metathesis then oxonium ylide formation–[2,3] sigmatropic rearrangement from diazo ether **10** and methacrolein (**11**), followed by chemoselective aldehyde reduction, lactonisation and dehydrogenation (Scheme 3).[7] In critically reviewing this first-generation synthesis, we identified several important areas for further investigation: First, was to render the strategy an asymmetric one; secondly, to develop an alternative to the difficult cross-metathesis using methacrolein (100 equiv), which likely contributes to the modest overall yield for the three-step sequence from diazo ether **10** to lactol **15** by way of oxonium ylide **13**. Thirdly, to analyse and understand in more detail the origins of selectivity in the key sigmatropic rearrangement (**13**→**14**), with the aim of increasing the efficiency/d.r. (80:20, desired isomer: minor isomers; the desired isomer is considered to originate from *endo*-selective rearrangement on the face of the ylide away from the phenyl group, as shown in **13**). And finally, to improve on the modest yield at the end of the synthesis, principally believed to due to slow dehydrogenation. This paper reports our promising results in these areas.

Results and Discussion

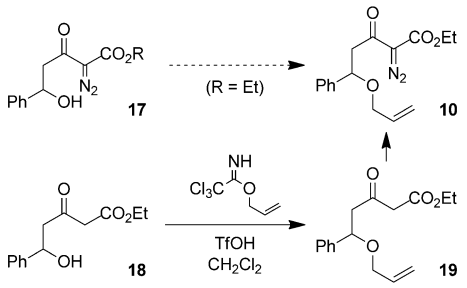
Racemic diazo ether **10** was originally prepared from a Lewis acid-catalysed Mukaiyama-type aldol reaction between [bis(allyloxy)methyl]benzene and the silyl enol ether of ethyl diazoacetoacetate,[7] and for which there was no direct asymmetric version.[7] However, a potentially straightforward asymmetric synthesis of diazo ether **10** was considered that involved allylation of the precursor diazoalcohol **17** (Scheme 4), as this alcohol has previously been shown by Kundu and Doyle to be available for R = Me in 80% yield and 95.5:4.5 e.r. by a catalytic asymmetric aldol reaction using benzaldehyde and the silyl enol ether of methyl α-diazoaceotacetate.[8] However, attempted allylation of *rac*-**17** (R = Et)[9] using allyl halides (Cl, Br, I) gave no diazo ether **10** (using K_2CO_3 as base), was complicated by multiple products (using NaH, or aq. NaOH/Bu_4NI), or gave $<50\%$ conversion with very low reproducibility when using allyl bromide/Ag_2O. Allyl trichloroacetimidate and catalytic TfOH (or $BF_3{\cdot}OEt_2$) also proved not to be viable, giving $<50\%$ diazo ether **10** which was contaminated with significant impurities including the corresponding α,β-unsaturated ketone from elimination of water.

As alcohol **18** is available in various levels of enantioenrichment by a variety of approaches,[10] we also considered its allylation to give ether **19** using allyl trichloroacetimidate-catalytic TfOH followed by diazo transfer.[11] In our hands, this allylation procedure gave an unworkable yield of 45% for ether **19** from *rac*-**18**,[12] which led us to consider alternative strategies for the asymmetric synthesis of diazo ether **10**, where the ether was in place in a β-allyloxycarbonyl-type compound, prior to homologation to the β-ketoester functionality.

In considering the challenge of an asymmetric acetate-like aldol reaction to directly generate β-alkoxycarbonyls, we

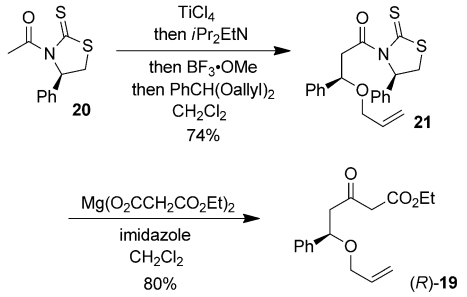


Scheme 3. Hodgson's 2008 oxonium ylide rearrangement-based synthesis of hyperolactone C (**1**).



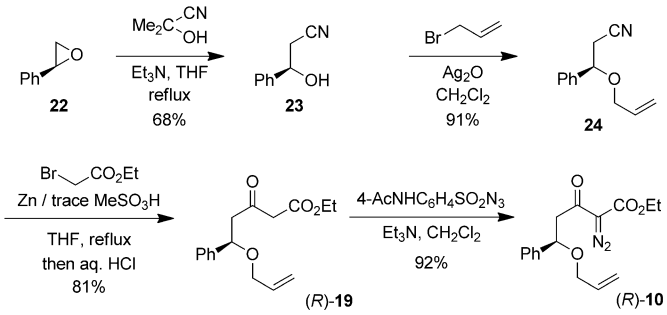
Scheme 4. Possible approaches to diazo ether **10**.

were attracted to the work of Romea and Urpí, who used the Lewis acid-induced reaction of acetals with titanium enolates of 4-substituted *N*-acetyl-1,3-thiazolidine-2-thiones.[13] In the present work using [bis-(allyloxy)methyl]benzene[14] as the acetal, then of the 4-substituted thiazolidinethiones (4-substitutent = Ph, Bn, *i*Pr, Me, or *t*Bu) and Lewis acids examined,[9] the (*R*)-phenylglycine-derived *N*-acyl thione **20** with $BF_3{\cdot}OMe_2$ proved optimal, giving a 86:14 d.r. of thione ethers with diastereomerically pure thione ether **21** being isolated in 74% yield after chromatography (Scheme 5). Interestingly, the *tert*-leucine-derived *N*-acyl thiazolidinethione (4-substitutent = *t*Bu) was less diastereoselective (76:24 d.r.) with this acetal, and similarly with benzaldehyde dimethyl acetal.[9] Masamune homologation[15] of thione ether **21** by using $Mg(O_2CCH_2CO_2Et)_2$–imidazole gave ether *R*-**19** in 80% yield with efficient (87%) recovery of the chiral auxiliary.



Scheme 5. Chiral auxiliary-based synthesis of ether (*R*)-**19**.

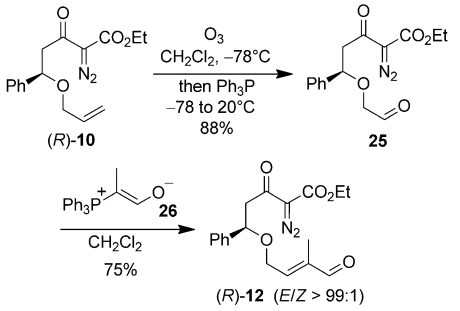
Although the thiazolidinethione chemistry discussed above provided access to ether (*R*)-**19** on small-scale, the requirement for careful chromatographic separation of thione ether **21** from the minor diastereomer led to examination of a further approach which avoided such a practically limiting issue. This last approach evaluated cyanide ring-opening of (*S*)-styrene oxide (**22**) followed by allylation and a Blaise reaction to give ether (*R*)-**19** (Scheme 6). After the optimisation described below and diazo transfer, this ultimately became the preferred route to diazo ether (*R*)-**10**. Regioselective ring-opening of (*S*)-styrene oxide[16] to give hydroxynitrile **23** was best achieved via a modified reaction with acetone cyanohydrin (68%),[17] although the corresponding unsaturated nitrile was identified as a side-product (10–15%). Using NaCN in $EtOH/H_2O$,[18] gave low yields (< 60%) and purity of hydroxynitrile **23**. Allylation of hydroxynitrile **23** was initially complicated by very low yields and reproducibility. As originally reported, reaction of hydroxynitrile **23** with allyl bromide in the presence of K_2CO_3 in acetone (72 h) provided a moderate yield (60%) of ether nitrile **24**,[19] but in our hands much lower yields (~35%) were obtained. Using NaH as base led to a mixture of products containing mainly the unsaturated nitrile from loss of water. Finally, in the presence of Ag_2O and a large excess of allyl bromide (10 equiv), ether nitrile **24** was obtained in excellent yield (91%). Interestingly, this last transformation required the presence of trace water for the reaction to proceed, with no reaction being observed in dry solvents (CH_2Cl_2, Et_2O, acetone). Formation of ether (*R*)-**19** from ether nitrile **24** was achieved by a modified Blaise reaction (81%).[20] The procedure benefited from simple in situ activation of zinc dust with $MeSO_3H$ and required only 2 equiv of ethyl bromoacetate, which minimised and avoided the formation of ethyl acetoacetate and diethyl butandioate by-products, respectively. Diazo transfer[11] with ether (*R*)-**19** gave diazo ether (*R*)-**10** in 92% yield.



Scheme 6. Synthesis of ether *R*-**10** from (*S*)-styrene oxide (**22**).

With an efficient asymmetric synthesis of diazo ether (*R*)-**10** established, we re-evaluated and sought improvements to the rest of our original racemic synthesis of hyperolactone C (**1**) (Scheme 3). The (*E*)-enal **12** substrate for oxonium ylide formation–rearrangement had previously been prepared in 21% yield from racemic diazo ether **10** by cross-metathesis using a large excess of methacrolein.[7] In the present study, ozonolysis followed by a Wittig olefination were found to give improved access to (*E*)-enal (*R*)-**12** (66% from diazo ether (*R*)-**10**, Scheme 7). The intermediate diazoaldehyde **25** was best obtained (88%) after ozonolysis by using 1 equiv of PPh_3 (use of Me_2S, or $(MeO)_3P$ were less satisfactory); the tolerance of the diazo group to this chemistry is noteworthy. High stereoselectivity ($E/Z > 99:1$) was seen in the Wittig olefination (75%), which was carried out using 1.3 equiv of the ylide **26** in CH_2Cl_2 (0.1 M in diazoaldehyde **25**) at RT for 50 h; a higher temperature (THF, reflux) led to traces (~2%) of *Z* isomer being detected, a lower con-

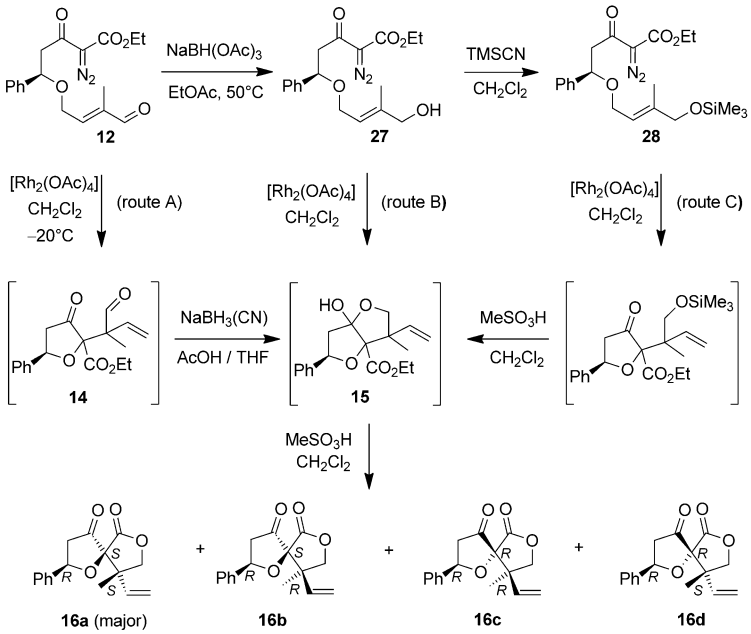
centration (0.01 M) led to longer reaction time or incomplete conversion even in refluxing CH_2Cl_2, whereas higher concentration (0.2 M) gave a decreased yield of (*E*)-enal **12** (65%).



Scheme 7. (*E*)-Enal (*R*)-**12** by ozonolysis–Wittig olefination of diazo ether (*R*)-**10**.

Access to the pure (*E*)-enal **12** allowed a more detailed study of the oxonium ylide formation–rearrangement chemistry (Scheme 8 and Table 1). Analysis was best carried out following reduction of the intermediate aldehyde **14** and, in an improvement to the original procedure, subsequent acid-catalysed[6] conversion of the resulting crude lactol mixture **15** to a mixture of dihydrohyperolactones **16a–d**, from which the major desired dihydrohyperolactone isomer **16a** could be isolated by chromatography. However, this sequence (route A) only led to **16a** in 33% yield over the 3 steps from (*E*)-enal **12**, with the **16a/16b/16c/16d** d.r. for the process being 79:13:6:2 (Table 1, entry 2).[9] A closer analysis of the crude reaction mixture after oxonium ylide rearrangement showed significant quantities of side-products in addition to the diastereomeric mixture of aldehyde **14**; the proportion (~25%) of these side-products was unaffected on using different catalysts ($[Rh_2(OAc)_4]$, $[Rh_2(oct)_4]$, or $[Rh_2(tfa)_4]$),[21] but a slight improvement (~3%) was observed if the reaction temperature was lowered (−20 °C). Although these side-products could not be characterised due their lability on silica gel, a major feature in the crude ^{1}H NMR indicated the preservation of allylaldehyde functionality (tm, $\delta = 6.60$, $J = 7.3$ Hz; $=CHCH_2$) which suggests that [1,2] rearrangements[22] from oxonium ylide **13** might be competing.

On the basis that the aldehyde functionality in (*E*)-enal **12** might be facilitating competing undesired [1,2] shift pathways by assisting homolysis in the putative intermediate oxonium ylide **13**, we decided to examine if efficiency in the oxonium ylide formation-rearrangement was improved by 1,2-reduction of (*E*)-enal **12** prior to ylide generation–rearrangement. Initially, reduction with $NaBH_3CN$/AcOH in THF at RT led to allylic alcohol **27** (82%) contaminated with side products likely formed by conjugate reduction, and chromatographic purification was required. The 1,2-reduction was best effected using a 1:1 mixture of $NaBH(OAc)_3$/AcOH in EtOAc at 50 °C which gave an almost quantitative yield and high purity of allylic alcohol **27** that could subsequently be used without further purification, giving dihydrohyperolactone **16a** in 53% isolated yield over the three steps from (*E*)-enal **12** (route B). Although the isolated yield of **16a** had improved, the change in **16a–d** d.r. from 79:13:6:2 to 65:3:28:4 in moving from (*E*)-enal **12** to allylic alcohol **27** (Table 1, entries 2 and 5) indicated that the latter displayed a significantly greater tendency to undergo competing oxonium ylide rearrangement to the undesired phenyl-bearing face (with high *endo* selectivity seen on both faces). While the factors that influence stereoselectivity in oxonium ylide rearrangements are not well understood, in the present case temporary capping of the alcohol as its silyl ether **28** for the ylide formation–rearrangement improved the proportion of desired dihydrohyperolactone **16a** at the expense of **16c** (**16a/16b/16c/16d** 75:3:18:4), giving **16a** in 63% yield from (*E*)-enal **12** (route C, 0.1 mmol scale; Table 1, entry 8). This latter sequence was used to prepare **16a** on 0.6 mmol scale (55% yield) to examine the last dehydrogenation step (see below).



Scheme 8. Routes A–C to dihydrohyperolactones **16a–d** from (*E*)-enal **12**.

Variation in the facial selectivity of the rearrangement due to whether allylic alcohol **27** or silyl ether **28** was employed led us to examine if such rearrangements also showed changes depending on ester group size (Table 1). As already noted above, facial selectivity was reduced with allylic alcohol **27** (67:33) compared with (*E*)-enal **12** (91:9), but interestingly the d.r. did vary for the corresponding Me and *t*Bu esters of **27** (71:3:22:4 and 50:2:44:4, respectively; Table 1, entries 4 and 6), indicating that face selectivity de-

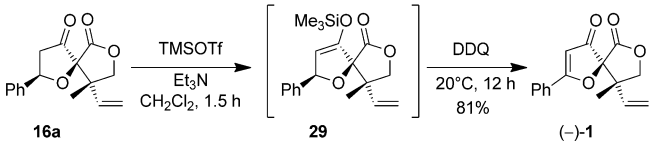
Table 1. Results for routes A–C in Scheme 8, and for the corresponding Me and *t*Bu ester series.[a]

Entry	Route	Ester	**16a** Yield [%][b]	**16a**	**16b**	**16c**	**16d**	Face selectivity[c]
1	**A**[d]	Me	(46)	74	19	4	3	93:7
2	**A**[d]	Et	(33)	79	13	6	2	92:8
3	**A**[d]	*t*Bu	(31)	78	12	5	5	90:10
4	**B**[e]	Me	(61)	71	3	22	4	74:26
5	**B**	Et	(53)	65	3	28	4	68:32
6	**B**	*t*Bu	(40)	50	2	44	4	52:48
7	**C**[e]	Me	(67)	81	4	12	3	85:15
8	**C**	Et	(63)	75	3	18	4	78:22
9	**C**	*t*Bu	(59)	72	2	23	3	74:26

[a] Ratio of **16a–d** determined by crude ^{1}H NMR analysis.[9] [b] Isolated yield, and based on (*E*)-enal **12** (or corresponding *E*-enal of Me/*t*Bu esters). [c] Selectivity for rearrangement occurring on opposite vs same face of ylide (cf. **13**) as Ph group. [d] Oxonium ylide formation–rearrangement carried out at −20 °C (24 h). [e] Same d.r. also observed at −20 °C.

creased with increasing ester group size (74:26 (Me ester), 68:32 (Et ester), 52:48 (*t*Bu ester). The same trend, but less pronounced, was observed in the Me/Et/*t*Bu ester series' corresponding to (*E*)-enal **12**, and silyl ether **28**.[23]

Dehydrogenation of dihydrohyperolactone **16** to hyperolactone C (**1**) had originally been achieved in poor conversion with DDQ under extended (6 d) reflux in benzene (Scheme 3),[7] and no improvement was seen in toluene. Activation of dihydrohyperolactone **16a** as the silyl enol ether **29** followed by addition of DDQ at RT,[24] proved a milder and more effective last step in the synthesis, giving hyperolactone C (−)-**1** in 81% yield (Scheme 9), with data consistent with the literature.[25]



Scheme 9. Completion of synthesis of hyperolactone C (−)-**1**.

Conclusion

In summary, we have completed an asymmetric synthesis of natural hyperolactone C (−)-**1** in 10 steps starting from (*S*)-styrene oxide. Key features include the use of the Blaise reaction to construct a diazo ether; subsequent chemoselective ozonolysis, in the presence of diazo functionality, is followed by Wittig olefination to give an *E*-enal. The *E*-enal is used in an improved oxonium ylide rearrangement, where factors influencing reaction efficiency and stereoselectivity have been identified. Conversion of the *E*-enal through a streamlined process involving 1,2-reduction, Rh^{II}-catalysed oxonium ylide formation–rearrangement and acid-catalysed lactonisation gives dihydrohyperolactone C in 53% yield involving no intermediate purifications. Finally, a mild and efficient DDQ oxidation proctol gives the natural product.

Experimental Section

The synthesis of hyperolactone C (−)-**1** from (*S*)-styrene oxide (**22**) is described below. Full details of all other experiments discussed above are given in the Supporting Information, which also includes ^{1}H and ^{13}C spectra for all compounds.

(*R*)-3-Hydroxy-3-phenylpropanenitrile (23): (*S*)-(−)-Styrene oxide 97% (**22**) (4.00 g, 33.3 mmol, 97% *ee*) and acetone cyanohydrin[26] (3.40 g, 40 mmol) were dissolved in THF (30 mL). Water (200 μL) and Et_3N (5.6 mL, 4.04 g, 40 mmol) were then added. The mixture was heated under reflux for 30 h and then concentrated under reduced pressure. The residue was purified by column chromatography (Et_2O/petrol 1:1) to give, as a yellow oil, hydroxynitrile **23** (3.32 g, 68%). $[\alpha]_D^{25} = +70$ ($c = 0.5$ in $CHCl_3$); lit.[27] $[\alpha]_D^{28} = +58$ ($c = 1.1$); R_f (Et_2O/petrol 1:1) = 0.21; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.46$–7.30 (m, 1H; Ar), 4.96 (t, $J = 6.2$ Hz, 1H; O-CH), 3.21 (brs, 1H; OH), 2.70 ppm (d, $J = 6.2$ Hz, 2H; CH_2); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 140.9$ (C, quat), 128.7 (2×Ar), 128.5 (Ar), 125.4 (2×Ar), 117.5 (C≡N), 69.6 (OCH), 27.7 ppm (CH_2); IR (neat): $\tilde{\nu}$ = 702, 757, 1028, 1057, 1087, 1220, 1309, 1412, 1455, 1495, 2255 (C≡N), 2900, 2930, 2969, 3033, 3065, 3089, 3443 cm^{-1}; LRMS (ESI$^+$): *m*/*z*: calcd for C_9H_9NNaO: 170.06; found: 170.07 [*M*+Na$^+$].

(*R*)-3-Allyloxy-3-phenylpropanenitrile (24): Hydroxynitrile **23** (3.31 g, 22.5 mmol) was dissolved in CH_2Cl_2 (56 mL). Silver(I) oxide (5.86 g, 25.3 mmol) and allyl bromide (19.5 mL, 27.2 g, 22.50 mmol) were added. The reaction mixture was stirred for 7 d at room temperature in the dark, then filtered and concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/petrol 2:3) to give, as a light yellow oil, ether nitrile **24**[19] (3.83 g, 91%) and (CH_2Cl_2/Et_2O 9:1) recovered starting alcohol **23** (0.21 g, 6%). R_f (EtOAc/petrol 1:9) = 0.37; R_f (CH_2Cl_2) = 0.51; $[\alpha]_D^{25} = +94$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.50$–7.31 (m, 5H; Ar), 5.99–5.82 (m, 1H; C*H*=CH$_2$), 5.29 (dd, $J = 17.3$, 0.9 Hz, 1H; O-CH_aH$_b$), 5.22 (d, $J = 10.4$ Hz, 1H; O-CH$_a$$H_b$), 4.64 (dd, $J = 7.2$, 5.7 Hz, 1H; Ar-C*H*), 4.01 (dd, $J = 12.8$, 4.9 Hz, 1H; = CH_aH$_b$), 3.85 (dd, $J = 12.8$, 6.2 Hz, 1H; =CH$_a$$H_b$), 2.80 (dd, $J = 16.7$, 7.3 Hz, 1H; NC-CH_aH$_b$), 2.71 ppm (dd, $J = 16.7$, 5.6 Hz, 1H; NC-CH$_a$$H_b$); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 138.8$ (C, quat.), 133.8 (=CH), 128.9 (2×Ar), 128.8 (Ar), 126.3 (2×Ar), 117.6 (=CH$_2$), 117.1 (C≡N), 76.2 (OCH), 69.8 (OCH$_2$), 27.0 ppm (NC-*C*H$_2$); IR (neat): $\tilde{\nu}$ = 702, 853, 930, 994, 1024, 1074, 1091, 1135, 1422, 1455, 1494, 1647, 2252 (C≡N), 2867, 2984, 3032, 3066 cm^{-1}; LRMS (ESI$^+$): *m*/*z*: calcd for: $C_{12}H_{13}NNaO$: 210.09; found: 210.09 [*M*+Na$^+$].

Ethyl (*R*)-5-(allyloxy)-3-oxo-5-phenylpentanoate (19): Zn powder (1.96 g, 30 mmol, dust < 10 μm, 98+%) was added to a solution of $MeSO_3H$ (43 mg, 0.45 mmol) in THF (30 mL) at room temperature. After heating under reflux for 10 min, a solution of ether nitrile **24** (18.7 g, 10 mmol) in THF (10 mL) was added in one portion. Then ethyl bromoacetate (2.20 mL, 3.32 g, 20 mmol) was added dropwise over 60 min. After heating under reflux for one additional hour, an aq. solution of HCl (50 mL, 2 M) was added at room temperature and the mixture was stirred for 90 min. The mixture was extracted with CH_2Cl_2 (5×50 mL). The combined extracts were washed with saturated aq. $NaHCO_3$ (30 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (EtOAc/petrol 1:9) to give, as a light yellow oil, ether **17** (2.23 g, 81%). $[\alpha]_D^{25} = +76$ ($c = 0.6$ in $CHCl_3$). R_f (EtOAc/petrol 1:9) = 0.22; ^{1}H NMR (400 MHz, $CDCl_3$): major tautomer $\delta = 7.28$–7.41 (m, 5H; Ar), 5.93–5.80 (m, 1H; C*H*=CH$_a$CH$_b$), 5.21 (dq, $J = 17.2$, 1.6 Hz, 1H; CH=CH_aCH$_b$), 5.15 (dq, $J = 10.4$, 1.4 Hz, 1H; C*H*= CH$_a$CH_b), 4.83 (dd, $J = 9.0$, 4.1 Hz, 1H; CHO), 4.18 (q, $J = 7.2$ Hz, 2H; CH$_3$CH_2), 3.89 (ddt, $J = 12.6$, 5.3, 1.4 Hz, 1H; CH_aCH$_b$O), 3.78 (ddt, $J = 12.6$, 6.1, 1.4 Hz, 1H; CH$_a$CH_bO), 3.49 (s, 2H; CH$_2$COOEt), 3.11 (dd, $J = 15.9$, 9.0 Hz, 1H; CH_aCH$_b$C=O), 2.73 (dd, $J = 15.9$, 4.1 Hz, 1H; CH$_a$CH_bC=O), 1.27 ppm (t, $J = 7.2$ Hz, 3H; CH$_3$), minor tautomer (~8%) $\delta = 4.99$ (s, 1H), 4.73 (dd, $J = 8.5$, 5.1 Hz, 1H; O-CH), 2.50 ppm (dd, $J = 14.3$, 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): major tautomer δ = 200.7 (C=O), 166.9 (O-C=O), 140.8 (Ar, quat), 134.4 (=CH), 128.6 (2× Ar), 128.0 (Ar), 126.5 (2×Ar), 117.0 (=CH$_2$), 77.1 (OCH), 69.6 (=C-*C*H$_2$-O), 61.3 (*C*H$_2$CH$_3$), 51.1 (CH$_2$), 50.3 (CH$_2$), 14.0 ppm (CH$_3$); IR (neat): $\tilde{\nu}$ =702, 759, 927, 1030, 1135, 1193, 1238, 1319, 1368, 1454, 1648, 1719,

1746, 2872, 2906, 2935, 2983, 3031, 3065 cm^{-1}; HRMS (ESI$^+$): *m/z*: calcd for $C_{16}H_{20}NaO_4$: 299.1254; found: 299.1253 [*M*+Na$^+$].

Ethyl (*R*)-5-(allyloxy)-2-diazo-3-oxo-5-phenylpentanoate (10): Et_3N (1.17 mL, 0.846 g, 8.36 mmol) was added to a solution of ether **17** (2.20 g, 7.96 mmol) and *p*-acetamidobenzensulfonylazide (2.0 g, 8.33 mmol) in dry CH_2Cl_2 (32 mL). After stirring for 24 h at room temperature, the mixture was concentrated under reduce pressure. The residue was triturated with a mixture of Et_2O/petrol 1:1 (4×30 mL). The combined solutions were concentrated under reduced pressure and the residue was purified by column chromatography (Et_2O/petrol 1:9) to give, as a light yellow oil, diazo ether **10**[7] (2.21 g, 92%). $[\alpha]_d^{25}=+10$ (*c*=0.5 in $CHCl_3$). R_f (Et_2O/petrol 1:9) = 0.18; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.41–7.28 (m, 5H; Ar), 5.93–5.80 (m, 1H; C*H*=CH$_a$H$_b$), 5.21 (dq, *J*=17.2, 1.7 Hz, 1H; =C*H*$_a$H$_b$), 5.14 (dq, *J*=10.4, 1.4 Hz, 1H; =CH$_a$*H*$_b$), 4.95 (dd, *J*=9.0, 4.2 Hz, 1H; OCH), 4.29 (q, *J*=7.1 Hz, 2H; CH_2CH_3), 3.91 (ddt, *J*=12.7, 5.1, 1.5 Hz, 1H; C*H*$_a$CH$_b$O), 3.80 (ddt, *J*=12.7, 6.0, 1.4 Hz, 1H; CH$_a$C*H*$_b$O), 3.58 (dd, *J*=16.3, 9.0 Hz, 1H; C*H*$_a$CH$_b$C=O), 3.01 (dd, *J*=16.3, 4.2 Hz, 1H; CH$_a$C*H*$_b$C=O), 1.32 ppm (t, *J*=7.1 Hz, 3H; CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ=189.9 (C=O), 161.1 (O=C-O), 141.2 (Ar, quat.), 134.7 (=CH), 128.4 (2×Ar), 127.8 (Ar), 126.7 (2×Ar), 116.7 (=CH_2), 76.7 (OCH), 69.6 (OCH_2), 61.4 (CH_2CH_3), 48.1 (O=CCH_2), 14.3 ppm (CH_3); IR (neat): $\tilde{\nu}$ = 702, 925, 1022, 1089, 1131, 1206, 1307, 1373, 1454, 1657, 1718, 2135, 2861, 2910, 2983, 3031, 3065 cm^{-1}; LRMS (ESI$^+$): *m/z*: calcd for $C_{16}H_{18}N_2NaO_4$: 325.12; found: 325.10 [*M*+Na$^+$].

Ethyl (*R*)-2-diazo-3-oxo-5-(2-oxoethoxy)-5-phenylpentanoate (25): A stream of ozone was bubbled through a solution of diazo ether **10** (302 mg, 1 mmol) in CH_2Cl_2 (33 mL) at −78°C. When the mixture turned blue, excess ozone was removed by a stream of oxygen then nitrogen. Ph_3P (262 mg, 1 mmol) was added at −78°C, and after stirring for ~20 h at room temperature, the solution was concentrated under reduced pressure. The residue was purified by column chromatography; gradient elution Et_2O/petrol 2:3 → Et_2O. Diazoaldehyde **25** was obtained as a light yellow oil (267 mg, 88%). R_f (Et_2O/petrol 2:3) = 0.07; R_f (Et_2O) = 0.49; $[\alpha]_D^{25}=+27$ (*c*=0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.67 (t, *J*=1.0 Hz, 1H; O=CH), 7.46–7.28 (m, 5H; Ar), 4.99 (dd, *J*=9.1, 3.8 Hz, 1H; O-CH), 4.31 (q, *J*=7.1 Hz, 2H; CH_2CH$_3$), 3.95 (t, *J*=1.0 Hz, 2H; O=CHCH_2), 3.68 (dd, *J*=16.6, 9.1 Hz, 1H; O-CHC*H*$_a$H$_b$), 3.07 (dd, *J*=16.6, 3.8 Hz, 1H; O-CHCH$_a$*H*$_b$), 1.33 ppm (t, *J*=7.1 Hz, 3H; CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ=200.8 (O=CH), 189.5 (C=O), 161.1 (O=C-O), 139.6 (Ar, quat.), 128.7 (2×Ar), 128.4 (Ar), 126.8 (2×Ar), 78.4 (O-CH), 74.2 (O=CH*C*H$_2$), 61.4 (*C*H$_2$CH$_3$), 47.8 (O-CH*C*H$_2$), 14.2 ppm (*C*H$_2$CH$_3$); IR (neat): $\tilde{\nu}$ = 702 (m), 729 (s), 1022 (s), 1133 (s), 1207 (s), 1309 (s), 1374 (s), 1653 (s), 1715 (s), 2137 (s), 2826 (w), 2909 (w), 2935 (w), 2984 (w), 3032 (w), 3063 cm^{-1} (w); HRMS (EI/EF$^+$): *m/z*: calcd for $C_{15}H_{17}N_2O_5$: 305.1132; found: 305.1179 [*M*+H$^+$].

Ethyl (*R*)-2-diazo-5-[(2*E*)-3-methyl-4-oxobut-2-enyloxy]-3-oxo-5-phenylpentanoate (12): A solution of diazoaldehyde **25** (267 mg, 0.88 mmol) and ylide **26** (363 mg, 1.14 mmol) in CH_2Cl_2 (8.8 mL) was stirred for 50 h at room temperature. The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography (Et_2O/petrol 3:7) to give, as a light yellow oil, (*E*)-enal **12**[7] (228 mg, 75%). R_f (Et_2O/petrol 4:6) = 0.39; $[\alpha]_D^{25}=17$ (*c*=0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.41 (s, 1H; CH=O), 7.42–7.28 (m, 5H; Ar), 6.57 (tq, *J*=5.6, 1.4 Hz, 1H; =CH), 4.96 (dd, *J*=9.4, 3.8 Hz, 1H; O-CH), 4.30 (q, *J*=7.2 Hz, 2H; O-CH_2CH$_3$), 4.22–4.17 (m, 2H; OCH_2CH=), 3.64 (dd, *J*=16.8, 9.4 Hz, 1H; O-CHC*H*$_a$CH$_b$), 3.00 (dd, *J*=16.8, 3.8 Hz, 1H; O-CHC*H*$_a$CH$_b$), 1.62 (m, *J*=1.2 Hz, 3H; =CCH$_3$), 1.33 ppm (t, *J*=7.2 Hz, 3H; O-CH$_2$C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ=194.5 (O=CH), 189.7 (C=O), 161.1 (O-C=O), 149.8 (=CH), 140.4 (C, quat.), 139.1 (C, quat.), 128.7 (2×Ar), 128.2 (Ar), 126.8 (2×Ar), 77.7 (O-CH), 65.5 (O-*C*H$_2$CH=), 61.5 (O-*C*H$_2$CH$_3$), 48.0 (O-CH*C*H$_2$), 14.3 (O-CH$_2$*C*H$_3$), 9.4 ppm (=C*C*H$_3$); IR (neat): $\tilde{\nu}$ = 702 (m), 746 (w), 1020 (m), 1095 (m), 1205 (m), 1308 (s), 1374 (m), 1453 (w), 1655 (s), 1691 (s), 1716 (s), 2137 (s), 2714 (w), 2834 (w), 2910 (w), 2984 (w), 3031 (w), 3063 cm^{-1} (w); LRMS (ESI$^+$): *m/z*: calcd for $C_{18}H_{20}N_2NaO_5$: 367.13; found: 367.11 [*M*+Na$^+$].

Ethyl (*R*)-2-diazo-5-[(2*E*)-3-methyl-4-hydroxybut-2-enyloxy]-3-oxo-5-phenylpentanoate (27): $NaBH(OAc)_3$ (0.70 g, 3.3 mmol) was added to a solution of (*E*)-enal **12** (228 mg, 0.66 mmol) and glacial AcOH (0.19 mL, 200 mg, 3.5 mmol) in EtOAc (18 mL). After heating for 5.5 h at ~50°C, water (18 mL) was added and the organic layer separated. The water layer was extracted with EtOAc (3×18 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (3×14 mL) and brine (1×14 mL). The solution was dried (Na_2SO_4) and concentrated under reduced pressure to give, as a pale yellow oil, allylic alcohol **27** (219 mg, 96%). R_f (Et_2O) = 0.50; $[\alpha]_D^{25}=+20$ (*c*=0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.42–7.27 (m, 5H; Ar), 5.62–5.54 (m, 1H; =CH), 4.91 (dd, *J*=9.0, 4.1 Hz, 1H; O-CH), 4.28 (q, *J*=7.2 Hz, 2H; CH_2CH$_3$), 4.00 (s, 2H; CH_2OH), 3.97–3.86 (m, 2H; =CHCH_2), 3.56 (dd, *J*=16.6, 9.0 Hz, 1H; OCHC*H*$_a$H$_b$), 2.99 (dd, *J*=16.6, 4.1 Hz, 1H; OCHCH$_a$*H*$_b$), 1.57 (s, 3H; =CCH_3), 1.31 ppm (t, *J*=7.2 Hz, 3H; CH$_2$CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ=189.8 (C=O), 161.0 (O=C-O), 141.2 (C, quat.), 139.2 (C, quat.), 128.4 (2×Ar), 127.7 (Ar), 126.7 (2×Ar), 121.3 (=CH), 76.6 (OCH), 67.8 (CH_2OH), 64.7 (=CH*C*H$_2$), 61.3 (O*C*H$_2$CH$_3$), 48.1 (O=C*C*H$_2$), 14.2 (OCH$_2$*C*H$_3$), 13.7 ppm (=C*C*H$_3$); IR (neat): $\tilde{\nu}$ = 1017 (s), 1073 (s), 1133 (m), 1206 (s), 1307 (s), 1374 (s), 1454 (w), 1653 (s), 1716 (s), 2136 (s), 2771 (w), 2921 (m), 3031 (w), 3062 (w), 3086 (w), 3432 cm^{-1} (br); HRMS (ESI$^+$): *m/z*: calcd for $C_{18}H_{22}N_2NaO_5$: 369.1421; found: 369.1422 [*M*+Na$^+$].

Ethyl (*R*)-2-diazo-5-[(2*E*)-3-methyl-4-(trimethylsilyloxy)but-2-enyloxy]-3-oxo-5-phenylpentanoate (28): TMSCN (125 μL, 99 mg, 1 mmol) was added to a solution of allylic alcohol **27** (219 mg, ~0.63 mmol) in CH_2Cl_2 (1 mL) at room temperature. After stirring for 60 min, the reaction mixture was concentrated under reduced pressure (**CAUTION**: toxic gas liberated), to give, as a pale yellow oil silyl ether **28** (256 mg, 97%). $[\alpha]_D^{25}=+20$ (*c*=0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.41–7.25 (m, 5H; Ar), 5.58 (tm, *J*=6.6 Hz, 1H; =CH), 4.91 (dd, *J*=9.1, 4.3 Hz, 1H; O-CH), 4.28 (q, *J*=7.1 Hz, 2H; CH_2CH$_3$), 3.98 (s, 2H; CH_2OSi), 3.95–3.85 (m, 2H; =CHCH_2), 3.53 (dd, *J*=16.3, 9.0 Hz, 1H; OCHC*H*$_a$H$_b$), 3.02 (dd, *J*=16.4, 4.3 Hz, 1H; OCHCH$_a$*H*$_b$), 1.51 (s, 3H; =CHCH_3), 1.31 (t, *J*=7.1 Hz, 3H; CH$_2$CH_3), 0.12 ppm (s, 9H; $SiCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ=189.9 (C=O), 161.2, (O=C-O), 141.4 (C, quat.), 138.3 (C, quat.), 128.4 (2×Ar), 127.7 (Ar), 126.8 (2×Ar), 121.2 (=CH), 76.9 (OCH), 67.7 (CH_2OSi), 65.0 (=CH*C*H$_2$), 61.4 (O*C*H$_2$CH$_3$), 48.2 (O=C*C*H$_2$), 14.3 (OCH$_2$*C*H$_3$), 13.6 (=C*C*H$_3$), −0.5 ppm ($SiCH_3$); IR (neat): $\tilde{\nu}$ = 843 (m), 877 (m), 1019 (w), 1064 (m), 1206 (w), 1251 (w), 1307 (s), 1373 (m), 1660 (m), 1719 (s), 2135 (s), 2856 (w), 2927 (w), 2958 cm^{-1} (w); HRMS (ESI$^+$): *m/z*: calcd for $C_{21}H_{30}N_2NaO_5Si$: 441.1816; found: 441.1815 [*M*+Na$^+$].

(2*R*,5*S*,9*S*)-9-Methyl-2-phenyl-9-vinyl-1,7-dioxaspiro[4.4]nonane-4,6-dione (16a): [$Rh_2(OAc)_4$] (11.4 mg, 0.026 mmol) was added in one portion to a solution of silyl ether **28** (256 mg, 0.61 mmol) in dry CH_2Cl_2 (66 mL) at room temperature. After stirring for 2 h, $MeSO_3H$ (44 μL, 65 mg, 0.68 mmol) was added. After stirring overnight at room temperature, the reaction mixture was filtered through pad of celite and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/petrol 1:9). First eluted a yellow oil, an 86:14 mixture of **16c** and **16d** (27 mg, 15%);[9] R_f (Et_2O/petrol 1:4) = 0.25. Second eluted a yellow oil, dihydrohyperolactone C **16a** (99 mg, 60%, 55% from (*E*)-enal **12**). R_f (EtOAc/petrol 1:9) = 0.16; R_f (Et_2O/petrol 1:4) = 0.19; $[\alpha]_D^{25}=-59$ (*c*=0.5 in $CHCl_3$); lit.[3b] $[\alpha]_D^{25}=-59$ (*c*=0.52 in $CHCl_3$);[25] ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.58–7.51 (m, 2H; Ar), 7.46–7.32 (m, 3H; Ar), 6.00 (dd, *J*=17.4, 10.9 Hz, 1H; C*H*=CH$_2$), 5.43–5.38 (m, 2H; =CH$_2$), 5.35 (dd, *J*=10.0, 6.6 Hz, 1H; O-CH), 4.67 (d, *J*=8.6 Hz, 1H; O-C*H*$_a$H$_b$), 4.03 (d, *J*=8.6 Hz, 1H; O-CH$_a$*H*$_b$), 2.95 (dd, *J*=18.7, 6.6 Hz, 1H; O=C-C*H*$_a$H$_b$), 2.68 (dd, *J*=18.7, 10.0 Hz, 1H; O=C-CH$_a$*H*$_b$), 1.39 ppm (s, 3H; CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ=208.4 (C=O), 170.6 (O-C=O), 139.8 (Ar, quat.), 135.7 (C*H*=CH$_2$), 128.9 (2×Ar), 128.7 (Ar), 126.2 (2×Ar), 119.4 (=CH_2), 90.6 (C(O)*C*C(O$_2$), quat.), 78.6 (Ar*C*H), 73.7 (OCH_2), 48.6 (*C*CH$_3$), 45.0 (O=C*C*H$_2$), 18.7 ppm (CH_3); IR(neat): $\tilde{\nu}$ =700 (m), 732 (w), 767 (w), 936 (w), 1007 (m), 1056 (w), 1106 (s), 1171 (m), 1272 (w), 1368 (w), 1455 (w), 1751 (s), 1961 (s), 2918 (w), 2974 cm^{-1} (w); LRMS (ESI$^+$): *m/z*: calcd for $C_{16}H_{16}NaO_4$: 295.09; found: 295.10 [*M*+Na$^+$]. Last eluted a yellow oil, an 73:27 mixture of **16b** and **16a** (6 mg, 4%);[9] R_f (Et_2O/petrol 1:4) = 0.13.

(5*S*,9*S*)-9-Methyl-2-phenyl-9-vinyl-1,7-dioxaspiro[4.4]non-2-ene-4,6-dione (1) (hyperolactone C): Et_3N (21 μL, 15 mg, 0.15 mmol, freshly distilled from CaH_2) and TMSOTf (23 μL, 28 mg, 0.125 mmol) were successively added to a solution of dihydrohyperolactone C **16a** (27 mg, 0.1 mmol) in CH_2Cl_2 (4.5 mL) at room temperature. After stirring for 1.5 h, DDQ (45 mg, 0.2 mmol) was added in one portion. The reaction mixture was stirred overnight, then concentrated under reduced pressure. The residue was purified by column chromatography (Et_2O/petrol 3:7) to give, as a pale yellow solid, hyperolactone C (**1**) (22 mg, 81%). M.p. 106–110°C (lit.[1a] m.p. 104°C), *rac* m.p. 114–120°C (lit.[7] 101–102°C); R_f (Et_2O/petrol 3:7) = 0.14; R_f (Et_2O/petrol 4:6) = 0.25; $[\alpha]_D^{25} = -257$ ($c = 0.02$ in $CHCl_3$); lit.[3b] $[\alpha]_D^{25} = -273$ ($c = 0.69$ in $CHCl_3$); lit.[6] $[\alpha]_D^{20} = -237$ ($c = 0.10$ in $CHCl_3$); lit.[1b] $[\alpha]_D^{22} = -271$, ($c = 0.11$ in $CHCl_3$); $[\alpha]_D^{25} = -264$ ($c = 0.01$ in EtOH); lit.[3b] $[\alpha]_D = -356$ ($c = 0.02$ in EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.89$–7.80 (m, 2H; Ar), 7.65–7.57 (m, 1H; Ar), 7.56–7.46 (m, 2H; Ar), 5.99 (dd, $J = 17.6$, 10.9 Hz, 1H; C*H*=CH_2), 5.99 (s, 1H; Ar-C=C*H*), 5.27 (d, $J = 10.9$ Hz, 1H; CH=CH_aH_b), 5.26 (d, $J = 17.6$ Hz, 1H; CH=CH_aH_b), 4.96 (d, $J = 8.6$ Hz, 1H; O-CH_aH_b), 4.12 (d, $J = 8.6$ Hz, 1H; O-CH_aH_b), 1.53 ppm (s, 3H; CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta =$ 196.5 (C=O), 187.2 (Ar-*C*=CH), 168.1 (CO_2), 134.2 (*C*H=CH_2), 133.6 (Ar), 129.0 (2×Ar), 127.7 (Ar, quat.), 127.4 (2×Ar), 119.1 (CH=*C*H_2), 100.2 (=*C*H-C=O), 93.1 (C(O)*C*C(O_2), quat.), 74.1 (O-CH_2), 48.8 ppm (CCH_3, quat.), 19.5 (CH_3); IR (KBr): $\tilde{\nu} = 775$ (m), 870 (m), 1101 (s), 1345 (m), 1607 (m), 1706 (s), 1781 (s), 1919 (w), 2986 (w), 3004 (w), 3025 (w), 3116 cm^{-1} (w); LRMS (ESI$^+$): *m*/*z*: calcd for $C_{16}H_{14}NaO_4$: 293.08; found: 293.06 [*M*+Na$^+$].

Acknowledgements

We thank the European Union for a Marie Curie Fellowship (PIEF-GA-2009-237270 to S.M.), and Professor T. Yakura (Toyama University) for some details on the preparation of the methyl esters of **10** and **19**.

[1] a) Y. Aramaki, K. Chiba, M. Tada, *Phytochemistry* **1995**, *38*, 1419–1421; b) S. L. Crockett, W. Schühly, F. Belaj, I. A. Khan, *Acta Crystallogr. Sect. E* **2004**, *60*, o2174–o2176; c) W. Schühly, S. L. Crockett, W. M. F. Fabian, *Chirality* **2005**, *17*, 250–256.

[2] N. Tanaka, M. Okasaka, Y. Ishimaru, Y. Takaishi, M. Sato, M. Okamoto, T. Oshikawa, S. U. Ahmed, L. M. Consentino, K.-H. Lee, *Org. Lett.* **2005**, *7*, 2997–2999.

[3] a) K. C. Nicolaou, D. Sarlah, D. M. Shaw, *Angew. Chem.* **2007**, *119*, 4792–4795; *Angew. Chem. Int. Ed.* **2007**, *46*, 4708–4711; b) K. C. Nicolaou, T. R. Wu, D. Sarlah, D. M. Shaw, E. Rowcliffe, D. R. Burton, *J. Am. Chem. Soc.* **2008**, *130*, 11114–11121; see also: c) K. C. Nicolaou, S. Sanchini, T. R. Wu, D. Sarlah, *Chem. Eur. J.* **2010**, *16*, 7678–7682; d) K. C. Nicolaou, S. Sanchini, D. Sarlah, G. Lu, T. R. Wu, D. K. Nomura, B. F. Cravatt, B. Cubit, J. C de La Torre, D. R. Burton, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 6715–6720.

[4] T. Ueki, M. Doe, R. Tanaka, Y. Morimoto, K. Yoshihara, T, Kinoshita, *J. Heterocycl. Chem.* **2001**, *38*, 165–172.

[5] G. A. Kraus, J. Wei, *J. Nat. Prod.* **2004**, *67*, 1039–1040.

[6] a) C. Du, L. Li, Y. Li, Z. Xie, *Angew. Chem.* **2009**, *121*, 7993–7996; *Angew. Chem. Int. Ed.* **2009**, *48*, 7853–7856 (corrigendum: C. Du, L. Li, Y. Li, Z. Xie, *Angew. Chem.* **2009**, *121*, 9375; *Angew. Chem. Int. Ed.* **2009**, *48*, 9211); b) Y. Wu, C. Du, C. Hu, Y. Li, Z. Xie, *J. Org. Chem.* 2011, 76, 4075–4081.

[7] D. M. Hodgson, D. Angrish, S. P. Erickson, J. Kloesges, C. H. Lee, *Org. Lett.* **2008**, *10*, 5553–5556.

[8] K. Kundu, M. P. Doyle, *Tetrahedron: Asymmetry* **2006**, *17*, 574–577.

[9] See the Supporting Information for details.

[10] a) S. Kiyooka, M. A. Hena, *J. Org. Chem.* **1999**, *64*, 5511–5523; b) R. Villano, M. De Rosa, C. Salerno, A. Soriente, A. Scettri, *Tetrahedron: Asymmetry* **2002**, *13*, 1949–1952; c) M. Hayashi, T. Inoue, Y. Miyamoto, N. Oguni, *Tetrahedron* **1994**, *50*, 4385–4398; d) M. Hayashi, K. Yoshimoto, N. Hirata, K. Tanaka, N. Oguni, K. Harada, A. Matsushita, Y. Kawachi, H. Sasaki, *Isr. J. Chem.* **2001**, *41*, 241–246; e) K. Narkunan, B.-J. Uang, *Synthesis* **1998**, 1713–1714.

[11] T. Yakura, K. Matsui, K. Matsuzaka, M. Yamashita, *Heterocycles* **2009**, *79*, 353–358. In this paper, both allylation, using allyl trichloroacetimidate, and diazo transfer have been reported on the corresponding Me ester of **18**; yields of ~50% and >90%, respectively were indicated in correspondence from Professor Yakura.

[12] C. Xu, C. Yuan, *Tetrahedron* **2005**, *61*, 2169–2186.

[13] a) A. Cosp, P. Romea, F. Urpí, J. Vilarrasa, *Tetrahedron Lett.* **2001**, *42*, 4629–4631; b) A. Cosp, I. Larrosa, I. Vilasís, P. Romea, F. Urpí, J. Vilarrasa, *Synlett* **2003**, 1109–1112; c) J. Baiget, A. Cosp, E. Gálvez, L. Gómez-Pinal, P. Romea, F. Urpí, *Tetrahedron* **2008**, *64*, 5637–5644; d) E. Gálvez, P. Romea, F. Urpí, *Org. Synth.* **2009**, *86*, 81–91.

[14] J. B. Brogan, J. E. Richard, C. K. Zercher, *Synth. Commun.* **1995**, *25*, 587–593.

[15] D. W. Brooks, L. D.-L. Lu, S. Masamune, *Angew. Chem.* **1979**, *91*, 76–77; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 72–74.

[16] Styrene oxide is readily (commercially) available in high e.r. by Jacobsen hydrolytic kinetic resolution: S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315.

[17] a) D. Mitchell, T. M. Koenig, *Tetrahedron Lett.* **1992**, *33*, 3281–3284; b) D. Mitchell, T. M. Koenig, *Synth. Commun.* **1995**, *25*, 1231–1238.

[18] A. Kamal, G. B. R. Khanna, R. Ramu, *Tetrahedron: Asymmetry* **2002**, *13*, 2039–2051.

[19] D.-Y. Ma, D.-X. Wang, J. Pan, Z.-T. Huang, M.-X. Wang, *Tetrahedron: Asymmetry* **2008**, *19*, 322–329.

[20] H. Shin, B. S. Choi, K. K. Lee, H.-W. Choi, J. H. Chang, K. W. Lee, D. H. Nam, N.-S. Kim, *Synthesis* **2004**, 2629–2632.

[21] Catalyst dependent d.r. has been observed in the oxonium ylide formation-[2,3] sigmatropic rearrangement of the corresponding Me ester of diazo ether **10**, see ref. [11].

[22] *Nitrogen, Oxygen and Sulfur Ylide Chemistry* (Ed.: J. S. Clark), Oxford University Press, Oxford, **2002**, pp. 1–113.

[23] Little variation in d.r. values are also observed for oxonium ylide formation–rearrangement of Me/Et/*t*Bu esters corresponding to diazo ether **10** (91:9,[11] 90:10,[7] and 87:13, respectively).

[24] a) I. Ryu, S. Murai, Y. Hatayama, N. Sonoda, *Tetrahedron Lett.* **1978**, *19*, 3455–3458; b) C.-L. Chin, D. D.-P. Tran, K.-S. Shia, H.-J. Liu, *Synlett* **2005**, 417–420.

[25] Conversion of **16a** to (−)-**1** and comparison of the data (in particular ^{1}H NMR: δ CH_2O) for **16a–d** with the dihydrohyperolactone reported in ref. [3b], indicates that the configuration drawn at the Ph-bearing centre in the latter should be corrected by inversion.

[26] R. F. B. Cox, R. T. Stormont, *Org. Synth.* **1935**, *15*, 1–2.

[27] P. N. Liu, P. M. Gu, F. Wang, Y. Q. Tu, *Org. Lett.* **2004**, *6*, 169–172.

Received: April 8, 2011
Published online: July 15, 2011

