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PAPER

Regioselective and stereoselective cyclizations of cyclohexadienones tethered to active methylene groups†

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The cyclization of 2,5-cyclohexadienones tethered to activated methylene groups was studied. The substitution around the cyclohexadienone ring serves to regioselectively direct these cyclizations based primarily on electronic effects. In the case of brominated substrates, these reactions proceed to give highly unusual electron-deficient tricyclic cyclopropanes. By using a *Cinchona* alkaloid-based phase-transfer catalyst, prochiral cyclohexadienones can be desymmetrized with moderate stereoselectivity.

Introduction

Cyclohexadienones are highly useful synthetic intermediates:[1] their ease of preparation from phenols and their versatile reactivity make them attractive intermediates for natural product synthesis[2] and drug discovery efforts.[3] Despite the progress that has been made investigating the reactivity of this class of compounds, there are still several areas that need further development. For instance, the influence of various substituents on the regioselectivity of conjugate additions into the dienone moiety has not been the subject of systematic work. While examples of regioselective conjugate additions do exist,[4] the underlying factors responsible for selectivity are often unclear. Gaining additional insight into this matter will undoubtedly prove useful for synthetic planning.

Another area that has seen only limited work is the enantioselective desymmetrization[5] of prochiral cyclohexadienones.[6] Such reactions are attractive for several reasons. The desymmetrization event will not only set the configuration of the fully substituted carbon atom, but under most circumstances will also result in the concomitant installation of a second contiguous stereocenter (and possibly more). Additionally, the symmetry-breaking event will leave behind an enone moiety that can be engaged in further synthetic manipulations.[7] Lastly, the desymmetrization of 2,5-cyclohexadienones could serve as a solution to the problems associated with the direct enantioselective dearomatization of phenols. While progress has been made in carrying out enantioselective oxidations at the *ortho*-position,[8,9] these methods have yet to be demonstrated for oxidations that occur at the *para*-position (*i.e.*, for the synthesis of 2,5-cyclohexadienones).

Our group has recently reported a Pd-catalyzed cyclization of alkyne-tethered cyclohexadienones.[10] During this work, we found that the cyclization of chiral, albeit racemic, substrates proceeds with predictable regioselectivity. We concluded that this regioselectivity was primarily due to steric effects and that the vinyl Pd intermediate generated during the reaction would preferentially bind to the less hindered C–C double bond. We questioned whether this same regioselectivity would be observed if the cyclization was changed such that an anionic intermediate was employed. Additionally, we were interested in the extension of this cyclization to include the desymmetrization of prochiral substrates by using a chiral phase-transfer catalyst (PTC). The desymmetrized products would allow access to bicyclic lactones that are found in natural products such as sorbicillactone A[11] and 5-bromoochrephilone[12] (Fig. 1). Herein we report our efforts aimed at studying the reaction scope and regioselectivity of intramolecular cyclizations of cyclohexadienones tethered to

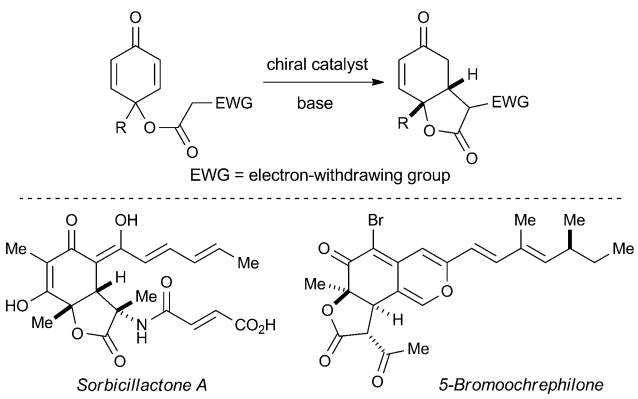

Fig. 1 Desymmetrization of EWG-tethered cyclohexadienones and potential synthetic targets.

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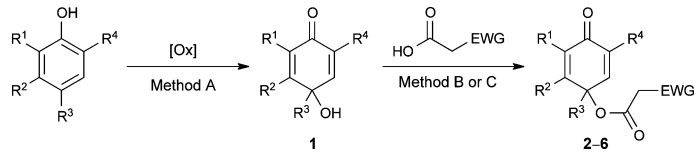
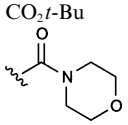
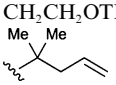
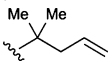
† Electronic supplementary information (ESI) available: optimization of desymmetrization reaction, synthesis and characterization data for all compounds, copies of ^{1}H and ^{13}C NMR spectra, chiral HPLC traces for enantioenriched products, and crystallographic data for **12r**. CCDC reference numbers 837018. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06125a

Table 1 Preparation of substrates[a]



Entry	Quinol	R^1	R^2	R^3	R^4	Method (yield)	Ester	EWG	Method (yield)
1							**2**	CO_2allyl	B (66%)
2							**3**	CO_2Bn	B (63%)
3							**4a**	CO_2t-Bu	B (43%)
4	**1a**	H	H	Me	H	—[14]	**5**		C (96%)
5							**6**		C (57%)[b]
6	**1b**	H	H	Ph	H	—[15]	**4b**	CO_2t-Bu	B (36%)
7	**1c**	H	H	*i*-Pr	H	A[16] (73%)	**4c**	CO_2t-Bu	B (56%)
8	**1d**	H	H	CH_2CO_2Me	H	A[17] (40%)	**4d**	CO_2t-Bu	B (38%)
9	**1e**	H	H	$CH_2C(CH_3)_3$	H	A (31%)	**4e**	CO_2t-Bu	C (>99%)
10	**1f**	H	H	CH_2CH_2OTBS	H	—[18]	**4f**	CO_2t-Bu	C (74%)
11	**1g**	H	H		H	A (37%)	**4g**	CO_2t-Bu	C (50%)
12	**1h**	Me	H	Me	Me	A[14] (78%)	**4h**	CO_2t-Bu	C (>99%)
13	**1i**	$SiMe_3$	H	Me	$SiMe_3$	A[c] (67%)	**4i**	CO_2t-Bu	C (86%)
14	**1j**	Me	OMe	Me	H	A (80%)	**4j**	CO_2t-Bu	C (98%)
15	**1k**	Me	H	Me	H	A (74%)	**4k**	CO_2t-Bu	C (95%)
16	**1l**	H	Me	Me	H	A (48%)	**4l**	CO_2t-Bu	C (73%)
17	**1m**	$SiMe_3$	H	Me	H	A[c] (51%)	**4m**	CO_2t-Bu	C (82%)
18	**1n**	H	H	Me	Br	A (76%)	**4n**	CO_2t-Bu	B (69%)
19	**1o**	H	Me	Me	Br	A (74%)	**4o**	CO_2t-Bu	C (96%)
20	**1p**	Me	OMe	Me	Br	A (51%)	**4p**	CO_2t-Bu	C (55%)
21	**1q**	Br	H	Me	Br	—[19]	**4q**	CO_2t-Bu	C (>99%)
22	**1r**	Br	H	*i*-Pr	Br	A (78%)	**4r**	CO_2t-Bu	C (95%)
23	**1s**	Br	H		Br	A (74%)	**4s**	CO_2t-Bu	C (81%)
24	**1t**	Br	H	CH_2CH_2OTBS	Br	A[c] (42%)	**4t**	CO_2t-Bu	C (96%)

[a] Method A: $PhI(OAc)_2$, CH_3CN, H_2O. Method B: HO_2CCH_2EWG, TFAA, then **1**, DME. Method C: DCC, DMAP, **1**, CH_2Cl_2. All yields are following purification using silica gel chromatography. See experimental section for more details. [b] After oxidation of the corresponding sulfide. [c] Acetone–H_2O used as solvent.

activated methylene groups and our initial efforts aimed at the desymmetrization of cyclohexadienones with a chiral PTC.

Results and discussion

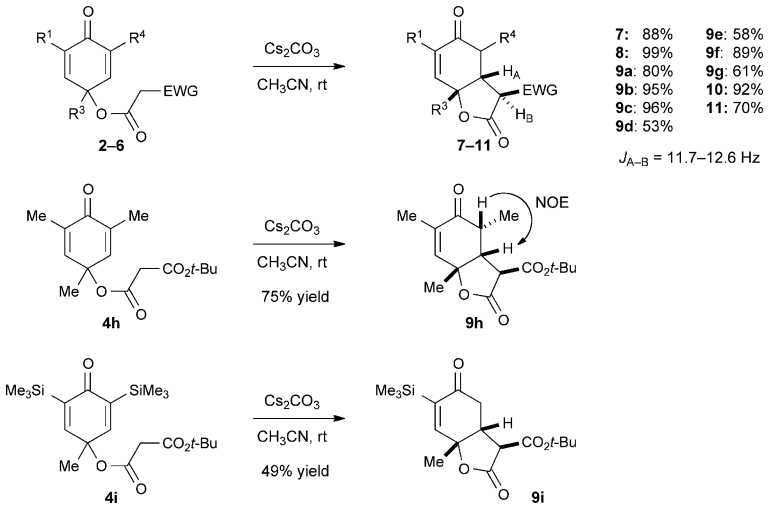
Substrate synthesis

All substrates used for our studies were prepared in two steps from the corresponding phenols; $PhI(OAc)_2$ oxidation was followed by coupling of the resulting quinols to malonic acid monoesters or other activated methylene compounds. This was initially accomplished with a trifluoroacetic anhydride-mediated coupling of the tertiary alcohol with the malonic acid monoester;[13] however, the use of DCC was later found to be more convenient and cost effective, particularly on larger scales. These reactions are applicable to a wide range of substrates (Table 1), including those with sterically demanding R^3 substituents (entries 7, 9, 11, 22, 23). Malonates with orthogonal protecting groups are tolerated (entries 1, 2, 3) as well as other electron-withdrawing groups such as amides (entry 4) and sulfones (entry 5).

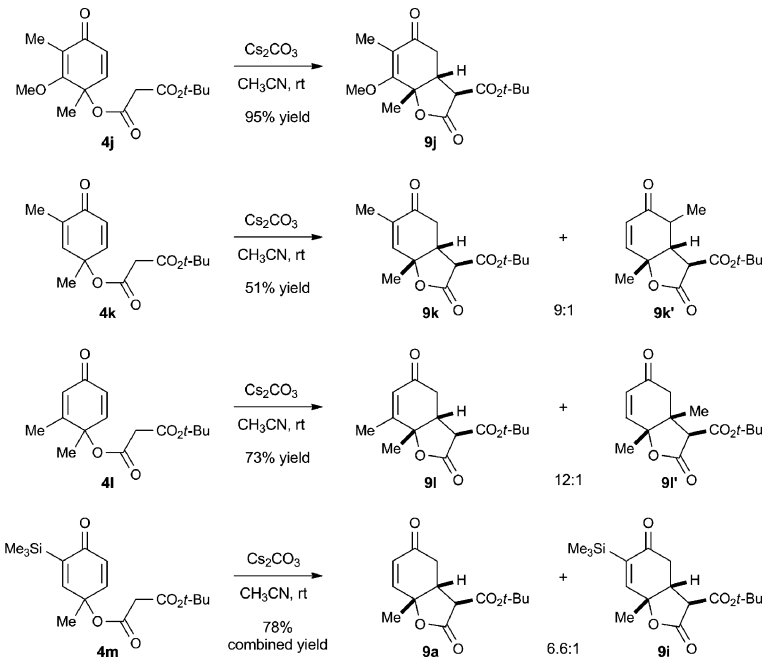
Cyclization of symmetric substrates

Despite the base sensitivity that cyclohexadienones generally exhibit,[1a] the cyclization of the *para*-substituted‡ dienones **2**, **3**, **4a–4g**, **5**, and **6** proceeded well with Cs_2CO_3 in CH_3CN (Scheme 1). Even in cases where steric problems might arise (*e.g.*, **4c**, **4e**, and **4g**), cyclization occurred efficiently. Substrate **4d** is also notable, as the potential problem of tertiary carboxylate elimination was not observed. In all cases, the bicyclic lactone product was isolated as a single diastereomer. The *cis*-fused ring system was confirmed by NOE experiments on **7** and **9h** (see the ESI for details†), while the configuration of the stereocenter bearing the electron-withdrawing group was assigned through coupling constant analysis. At this

‡ For substitution patterns around the cyclohexadienones, we utilize nomenclature from the corresponding phenols.



Scheme 1 Cyclization of symmetric substrates.



Scheme 2 Regioselective cyclizations.

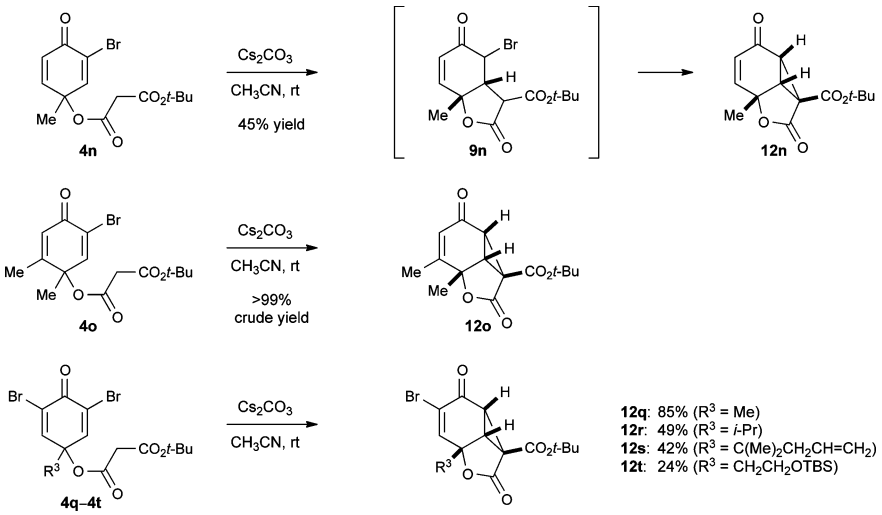
time, it is not clear if a second diastereomer also forms during the reaction and then epimerizes under the reaction or isolation conditions.

ortho-Disubstituted cyclohexadienones also underwent cyclization successfully. In the case of **4h**, the product **9h** contains four contiguous stereocenters and was formed as a single diastereomer. Although disilane **4i** did cyclize successfully, the product contained only one trimethylsilyl group. This is not surprising as α-silyl ketones are known to undergo facile protodesilylation.[20]

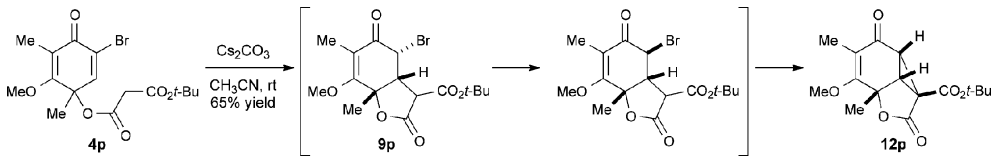
Regioselective cyclizations

We were interested in examining the influence of various substituents on the regioselectivity of these anionic reactions (Scheme 2). The cyclization of *meta*-methoxy substrate **4j** was completely regioselective and afforded **9j** (an intermediate used in our synthesis of sorbicillactone A[21]) in high yield. This result can most simply be explained by electronic effects, as one olefin of the cyclohexadienone can be considered to be a vinylogous ester and, consequently, less electrophilic.

The methylated substrates **4k** and **4l** cyclized with very good regioselectivity, but also raised questions as to whether this effect is electronic or steric in nature. Compound **4k**, with the methyl group α to the ketone, cyclized with a regioselectivity of 9 : 1. This is in agreement with an observation made by Giomi and co-workers concerning the addition of diethyl malonate to an *ortho*-methyl-substituted dienone.[22] Higher regioselectivity (12 : 1) was observed in the cyclization of **4l** to **9l**, where the methyl group is in the β position. This dependence could easily be attributed to steric effects; however, an electronic argument involving the weakly electron-donating nature of methyl substituents should not be discounted.



Scheme 3 Cyclization of brominated substrates.



Scheme 4 Cyclization of **4p**.

Finally, we chose to investigate vinyl silane **4m**. Considering a purely steric model, the increased bulk of the trimethylsilyl group in **4m** as compared to the methyl group in **4k** should increase selectivity. Similarly, the lower group electronegativity of $SiMe_3$ (2.06)[23] relative to CH_3 (~2.3)[24] would also be expected to give rise to higher regioselectivity. However, the cyclization of **4m** actually afforded product **9a** as the major product (6.6 : 1 ratio of **9a** and **9i**). In this case, compound **9a** is the product of conjugate addition onto the silicon-bearing olefin, followed by protodesilylation. This reversal in selectivity can be attributed to silicon's ability to stabilize an adjacent negative charge,[25] while the aforementioned electronegativity difference likely explains why complete selectivity is not observed.

Cyclization of brominated substrates

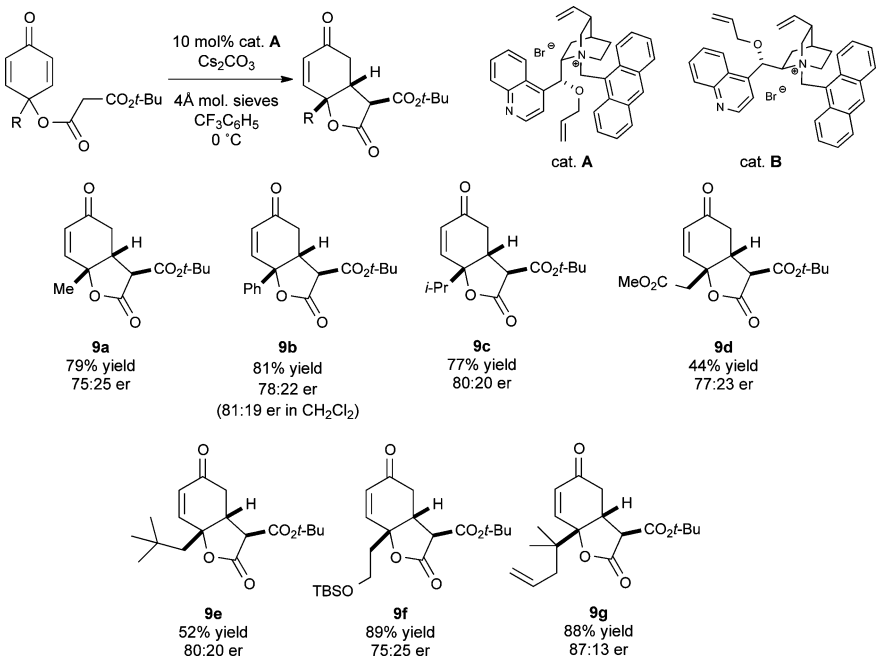
If the regioselectivity observed during the cyclizations described in the previous section was indeed strongly influenced by electronic effects, then it stands to reason that the presence of an electron-withdrawing group on the cyclohexadienone should reverse the observed regioselectivity. In other words, an anionic nucleophile should preferentially attack the olefin bearing the electron-withdrawing group. We found bromine to be particularly attractive in that it is easily installed, usually has a positive impact in terms of chemical yield on the oxidative dearomatization step, and serves as a useful handle for further synthetic transformations.

When the bromine-containing substrate **4n** was subjected to our cyclization conditions, the tricyclic cyclopropane **12n** was obtained (Scheme 3). While this was an unexpected outcome, there have been numerous examples in the literature of similar cyclopropanations.[26,27] Importantly, the conjugate addition required to initiate the cyclopropanation pathway occurred with complete regioselectivity. We did not observe any products arising from addition into the less substituted double bond in **4n**. Similarly, substrate **4o** cyclized to give cyclopropane **12o** exclusively. This cyclopropanation could also be extended to the symmetric dibromides **4q–4t**.

Interestingly, while the cyclization of **4p** proceeded well, it was noticeably slower than the reaction of **4n** and **4o**. If the reaction of **4p** was terminated early, bromide **9p** could be isolated as a single diastereomer (Scheme 4). The configuration of the bromine-bearing stereocenter in **9p** does not allow for backside attack by the malonate. By resubjecting bromide **9p** to the reaction conditions (or allowing **4p** to react overnight), the complete reaction can be realized. Presumably, this occurs by epimerization of the relevant stereocenter. The slow epimerization of **9p** might be related to the pK_a difference between the α-bromoenones (*e.g.*, **7n**) formed during the reactions in Scheme 3 and the α-bromovinylogous ester contained in **9p**.

Cyclizations with *Cinchona* alkaloid catalysts

Recognizing that the symmetric dienones discussed above contain enantiotopic olefins, we hypothesized that a chiral phase-transfer catalyst might be able to desymmetrize these prochiral compounds. Asymmetric phase-transfer catalysis has proven to be a valuable tool for constructing enantioenriched products.[28] However, to the best of our knowledge, there have been no examples of enantioselective phase-transfer catalyzed desymmetrizations.[29] While we were confident that the desired cyclization would occur on only one face of the dienone, we expected the discrimination of the two enantiotopic olefins based solely on non-bonding interactions to be a significant challenge.



Scheme 5 Desymmetrization *via* phase-transfer catalysis.

We were attracted to the *Cinchona* alkaloid-based phase-transfer catalysts owing to their ready availability and ease of modification. Our efforts toward optimization included variations of the electronic and steric properties of the catalyst; modifications of the base, temperature, and solvent; and a brief survey of the malonate ester (substrates **2**–**4a**). The best reaction conditions were determined to be those shown in Scheme 5.† Importantly, when using catalyst **B**, the pseudo-enantiomer of catalyst **A**, the opposite enantiomer *ent*-**3c** was obtained with similar levels of enantioinduction.

We were concerned that the background reaction might be a competing process, which would lead to the diminished selectivity relative to other asymmetric phase-transfer reactions. Importantly, under otherwise identical conditions (1 equiv. Cs_2CO_3, CH_2Cl_2, 0 °C, 4 h), no conversion of **4a** to **9a** was observed. We also thought that the reaction might be reversible, again leading to lower selectivity. When isolated **9a** of 71 : 29 er was treated with catalyst **A** and Cs_2CO_3 over an extended reaction time (0 °C → r.t., 12 h), the product was isolated with 67 : 33 er. In a separate experiment, substrate **4a** was cyclized in the absence of catalyst (1 equiv. Cs_2CO_3) to give racemic **9a**. Catalyst **A** was then added and the reaction continued for another 12 h. In this case, only racemic product was isolated. While these experiments do not conclusively rule out the possibility of a reversible reaction, such a process does not seem to be important with rapid reaction times.

Interestingly, we observed increased enantioselectivity on substrates bearing more sterically demanding substituents at the *para* position of the cyclohexadienone ring (compounds **9b** to **9g**), and speculated that substituents in the *ortho* positions of the cyclohexadienone might offer similar steric benefits. In practice, desymmetrization of the dibromo compounds **4q**–**4t** produced enantioenriched cyclopropanes **12q**–**12t** (Fig. 2) with enantioselectivity that was improved relative to their desbromo counterparts, with the exception of **12s**, which showed reduced enantioselectivity

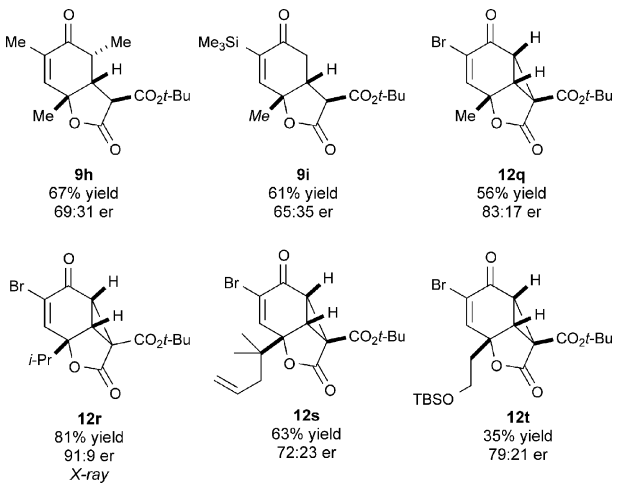


Fig. 2 Asymmetric cyclization products.

after the extended reaction time needed for complete conversion. Additionally, the absolute configuration of **12r** was determined by X-ray diffraction analysis.† Curiously, substrates **4h** and **4i** were poor substrates for these desymmetrization reactions, affording **9h** and **9i** with 69 : 31 and 65 : 35 er, respectively. These two reactions were noticeably slower than the others and required 36 h and 4 days, respectively, to reach complete conversion. At this point, it is not clear if the decreased enantioselectivity is due to catalyst decomposition over the prolonged reaction times or to poor interaction with the catalyst.

We also speculated that we might not be achieving optimal selectivity due to the fact that the malonate substrates are capable of forming two different reactive intermediates (*i.e.*, the enolate could form on the carbonyl of either ester). These two intermediates might have different interactions with the catalyst and therefore lead to different levels of enantioinduction. In an attempt to

address this, we performed the cyclization on substrates containing electron-withdrawing groups other than esters (compounds **5** and **6**). By introducing additional electronic differentiation, using amides or sulfones, we had hoped to favor the formation of only one reactive intermediate that could proceed to the cyclization event. Unfortunately, a decreased level of enantioselectivity was actually observed and products **10** and **11** (Fig. 3) were both obtained with a modest 68 : 32 er.

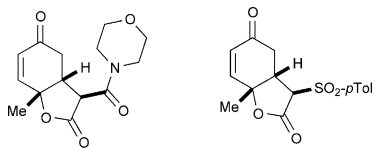
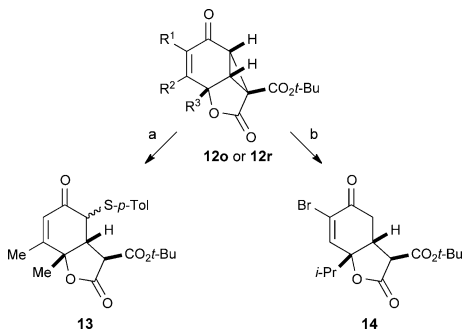


Fig. 3 Asymmetric cyclization products containing varied EWGs.

To further interrogate this problem, we were also interested in testing cyclohexadienone-tethered β-ketoesters, which would also be useful in the pursuit of natural products such as 5-bromoochrephilone. However, we were unable to obtain these compounds due to the facile decarboxylation of acetoacetic acid and its derivatives, as well as the propensity of the desired substrates to undergo rearomatization *via* Carroll rearrangement.[30]

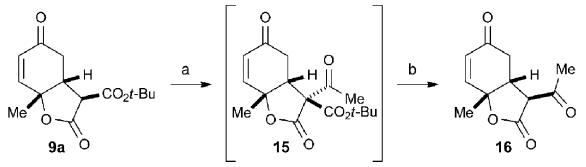
Further transformations of products

We have already begun to explore the utility of these bicyclic lactones as synthetic intermediates. The electron-deficient tricyclic cyclopropanes appear to be unknown in the literature and may prove to be valuable synthetic scaffolds as well.[31] For example, heating cyclopropane **12o** with toluenethiol in toluene produced the sulfide **13** as a ~2 : 1 mixture of epimers (Scheme 6). Alternatively, the cyclopropane ring of **12r** can be reductively cleaved[32] with SmI_2 to form **14**. Notably, the bromoenone moiety was left intact. Enone **14** is interesting in that it is formally the product of an enantioselective dearomatization/conjugate addition sequence. However, the occurrence of such a hypothetical conjugate addition does not seem probable as the cyclization would actually occur on the olefin bearing the bromine (*cf.*, Scheme 3).



Scheme 6 Elaboration of cyclopropane products **12o** and **12r**. Reagents and conditions: (a) **12o**, toluenethiol, toluene, 115 °C, 37% (from **4o**); (b) **12r**, 2.1 equiv. SmI_2, THF, 0 °C, 39% yield (yields not optimized).

In a final one-pot sequence, we have been able to address the problems associated with forming cyclization substrates containing β-ketoesters (Scheme 7). Deprotonation of malonate **9a** with



Scheme 7 Elaboration of **9a** to β-ketolactone **16**. Reagents and conditions: (a) NaH, AcCl, THF, 0 °C to r.t.; (b) TFA, 0 °C to r.t., 46% over two steps (not optimized).

NaH, followed by reaction with acetyl chloride, produced **15**, which upon acidic hydrolysis underwent rapid decarboxylation to give β-ketoester **16**.

Conclusions

In conclusion, we have shown that intramolecular conjugate additions of cyclohexadienones can proceed regioselectively. The selectivity of these cyclizations appears to be governed largely by electronic factors, although steric effects likely play a role in some cases. This is in contrast to our previously reported Pd-catalyzed cyclizations, which were controlled mainly by steric factors. Together, these observations will be important for synthetic planning and may prove to be a useful tool for elucidating the mechanisms of future reactions.

We have also shown that chiral phase-transfer catalysts can be used to desymmetrize prochiral cyclohexadienones. The fact that the *Cinchona* alkaloid catalysts are capable of differentiating the two enantiotopic olefins solely on the basis of non-bonding interactions is remarkable. Efforts are underway to improve the selectivity of this reaction and the results will be reported in due course.

Experimental

Materials and methods

Unless otherwise stated, reactions were performed in flame- or oven-dried glassware under an argon or nitrogen atmosphere using anhydrous solvents. Acetonitrile and CH_2Cl_2 were dried by passage through an activated alumina column under argon. Powdered 4 Å molecular sieves were activated by heating under vacuum and kept at 90 °C until use. Thin-layer chromatography (TLC) was performed using plates precoated with silica gel XHL w/UV254 (250 μm) or alumina W/UV and visualized by UV light or $KMnO_4$, phosphomolybdic acid, or anisaldehyde stains, followed by heating. Silica gel (particle size 32–63 μm) was used for flash chromatography. ^1H and ^{13}C NMR spectra are reported relative to the residual solvent peak (δ 7.26 and δ 77.2 for ^1H and ^{13}C, respectively). Data for ^1H NMR spectra are reported as follows: chemical shift (δ (ppm)) (multiplicity, coupling constant (Hz), integration). Spectra are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet. IR samples were prepared on NaCl plates either neat or by evaporation from $CHCl_3$ or CH_2Cl_2.

General method 1: cyclization using Cs_2CO_3 in MeCN

A solution of the appropriate substrate (1 equiv.) in MeCN (0.05 M in substrate) was treated with solid Cs_2CO_3 (2.5 equiv.).

The reaction mixture was stirred until consumption of the starting material (usually within 30 min for sterically unhindered substrates), and then concentrated and purified directly by flash-column chromatography.

General method 2: asymmetric cyclization using phase-transfer catalysis

A mixture of the cyclohexadienone substrate (1 equiv.), 4 Å molecular sieves (100% w/w), and catalyst **A** (10 mol%) was suspended in trifluorotoluene (0.05 M in substrate) and cooled to 0 °C. Cs_2CO_3 (1 equiv.) was added and the mixture was stirred until consumption of the starting material. In cases where no conversion was observed after ~4 h, the reaction mixture was allowed to gradually reach r.t. and stirred until consumption of the starting material. The solvent was then removed *in vacuo* and the products purified directly by flash-column chromatography.

(3*S*,3a*R*,7a*R*)-Allyl-7a-methyl-2,5-dioxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carboxylate (7)

Using a modification of general method 2, in which CH_2Cl_2 was used as solvent, $CsOH{\cdot}H_2O$ was used as a base, and the reaction temperature was −78 °C, **2** cyclized to give **7** in 75% yield after flash-column chromatography (3 : 1 hexanes–EtOAc). Chiral-phase HPLC analysis (Chiralcel OD, 3% ethanol in hexanes, 1.5 mL min^{-1}, λ = 225 nm) showed 65 : 35 er (RT_{major} = 22.3 min, RT_{minor} = 23.5 min). When crude **2** (obtained using general method B) was allowed to stand at −15 °C overnight, racemic **7** was obtained in 88% yield after chromatographic purification. **IR** (thin film) 2983, 2929, 1785, 1737, 1685, 1381, 1294, 1164, 1093, 998, 781 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.68 (dd, J = 10.3, 2.0 Hz, 1 H), 6.09 (d, J = 10.3 Hz, 1 H), 5.90 (dddd, J = 16.2, 10.5, 5.8, 5.8 Hz, 1 H), 5.38 (dq, J = 17.2, 1.4 Hz, 1 H), 5.28 (dd, J = 10.4, 1.1 Hz, 1 H), 4.77–4.62 (m, 2 H), 3.49 (d, J = 12.5 Hz, 1 H), 3.38–3.31 (m, 1 H), 2.75 (dd, J = 17.8, 5.3 Hz, 1 H), 2.64 (dd, J = 17.8, 1.6 Hz, 1 H), 1.72 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ 194.2 (C), 168.7 (C), 166.1 (C), 146.7 (CH), 131.0 (CH), 129.5 (CH), 119.6 (CH_2), 80.6 (C), 67.1 (CH_2), 51.5 (CH), 44.7 (CH), 35.9 (CH_2), 23.9 (CH_3); **HRMS** (ESI+) 273.0733 calcd for $C_{13}H_{14}O_5Na$, found 273.0729; the NOE correlation used to assign the relative stereochemistry of **7** is shown in Fig. 4.

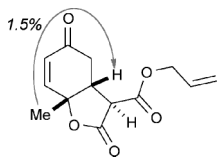


Fig. 4 NOE correlation for **7**.

(3*S*,3a*R*,7a*R*)-Benzyl-7a-methyl-2,5-dioxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carboxylate (8)

Using a modification of general method 2, in which CH_2Cl_2 was used as solvent and the reaction was started at −78 °C and gradually allowed to warm to r.t., **4b** cyclized to give **8** in 99% yield after flash-column chromatography (3 : 1 hexanes–EtOAc). Chiral-phase HPLC analysis (Chiralcel OD-H, 8% ethanol in hexanes, 1 mL min^{-1}, λ = 225 nm) showed ~racemic material (RT_{first} = 20.4 min, RT_{second} = 23.7 min). Also, using general method 1, racemic **8** was obtained in 91% yield. **IR** (thin film) 3059, 3032, 2910, 1778, 1731, 1679, 1378, 1291, 1158, 1090, 987 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39–7.36 (m, 5 H), 6.68 (dd, J = 10.4, 2.0 Hz, 1 H), 6.08 (d, J = 10.4 Hz, 1 H) 5.28 (d, J = 12.3 Hz, 1 H), 5.22 (d, J = 12.3 Hz, 1 H), 3.52 (d, J = 12.5 Hz, 1 H), 3.39–3.32 (m, 1 H), 2.74 (dd, J = 17.8, 5.3 Hz, 1 H), 2.63 (dd, J = 17.9, 2.3 Hz, 1 H), 1.73 (s, 3 H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ *C* 194.1 (C), 168.6 (C), 166.3 (C), 146.7 (CH), 134.8 (C), 129.5 (CH), 128.9 (CH × 2), 128.8 (CH), 128.4 (CH × 2), 80.6 (C), 68.3 (CH_2), 51.5 (CH), 44.7 (CH), 35.9 (CH_2), 23.9 (CH_3); **HRMS** (ESI+) 323.0890 calcd for $C_{17}H_{16}O_5Na$, found 323.0889.

(3*S*,3a*R*,7a*R*)-*tert*-Butyl-7a-methyl-2,5-dioxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carboxylate (9a)

Using general method 2, **4a** cyclized in 2 h to give **9a** in 79% yield after flash-column chromatography (5 : 1 hexanes–EtOAc). Chiral-phase HPLC analysis (Chiralcel OJ, 8% isopropanol in hexanes, 1 mL min^{-1}, λ = 225 nm) showed 75 : 25 er (RT_{major} = 20.4 min, RT_{minor} = 23.7 min). Using general method 1, racemic **9a** was obtained in 80% yield. **IR** (thin film) 2983, 2929, 1786, 1728, 1686, 1371, 1295, 1150, 1148, 1089, 983 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.67 (dd, J = 10.3, 1.6 Hz, 1 H), 6.08 (d, J = 10.3 Hz, 1 H), 3.35 (d, J = 12.3 Hz, 1 H), 3.32–3.29 (m, 1 H), 2.74 (dd, J = 17.8, 4.8 Hz, 1 H), 2.63 (d, J = 17.8 Hz, 1 H), 1.71 (s, 3 H), 1.49 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ 194.5 (C), 169.2 (C), 165.3 (C), 147.0 (CH), 129.4 (CH), 83.8 (C), 80.3 (C), 52.4 (CH), 44.5 (CH); 36.0 (CH_2), 28.1 (CH_3 × 3), 24.0 (CH_3); **HRMS** (ESI+) 289.1046 calcd for $C_{14}H_{18}O_5Na$, found 289.1056.

(3*S*,3a*R*,7a*R*)-7a-Methyl-3-(morpholine-4-carbonyl)-3a,4-dihydrobenzofuran-2,5(3*H*,7a*H*)-dione (10)

Using general method 2, **5** cyclized to give **10** in 87% yield after flash-column chromatography (2 : 1 hexanes–EtOAc). Chiral-phase HPLC analysis (Chiralcel OD, 10% ethanol in hexanes, 1 mL min^{-1}, λ = 225 nm) showed 68 : 32 er (RT_{minor} = 23.2 min, RT_{major} = 42.5 min). Using general method 1, racemic **10** was obtained in 92% yield. **IR** (thin film) 2971, 2859, 1773, 1681, 1645, 1441, 1297, 1242, 1113, 1094, 975 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.68 (dd, J = 10.3, 2.0 Hz, 1 H), 6.06 (d, J = 10.3, 1.0 Hz, 1 H), 4.00 (dt, J = 13.4, 3.0 Hz, 1 H), 3.82–3.57 (m, 6 H), 3.58 (d, J = 11.9 Hz, 1 H), 3.39–3.26 (m, 2 H), 2.72 (dd, J = 17.8, 5.5 Hz, 1 H), 2.54 (ddd, J = 17.9, 2.0, 1.1 Hz, 1 H), 1.72 (s, 3 H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ 195.2 (C), 169.9 (C), 162.4 (C), 147.1 (CH), 129.7 (CH), 80.9 (C), 66.9 (CH_2), 66.6 (CH_2), 48.5 (CH), 46.6 (CH_2), 43.7 (CH), 43.2 (CH_2), 36.2 (CH_2), 23.9 (CH_3); **HRMS** (ESI+) 302.0999 calcd for $C_{14}H_{17}NO_5Na$, found 302.1016.

(3a*S*,7a*R*)-7a-Methyl-3-tosyl-3a,4-dihydrobenzofuran-2,5(3*H*,7a*H*)-dione (11)

Using general method 2, **6** cyclized to give **11** in 90% yield after flash column chromatography (1 : 1 hexanes–EtOAc). Chiral-phase HPLC analysis (Chiralcel OD, 10% ethanol in hexanes, 1 mL min^{-1}, λ = 225 nm) showed 68 : 32 er (RT_{minor} = 27.9 min, RT_{major} = 32.0 min). Using general method 1, racemic **11** was obtained in 70% yield. **IR** (thin film) 2923, 1783, 1687, 1595, 1318, 1245, 1149, 1085, 965, 813 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.85 (d,

J = 8.4 Hz, 2 H), 7.39 (d, J = 8.1 Hz, 2 H), 6.61 (dd, J = 10.4, 1.8 Hz, 1 H), 6.06 (dd, J = 10.4, 0.9 Hz, 1 H), 3.94 (d, J = 11.6 Hz, 1 H), 3.55 (ddt, J = 11.6, 5.8, 2.0 Hz, 1 H), 3.18 (ddd, J = 17.9, 1.8, 1.1 Hz, 1 H), 2.82 (dd, J = 17.9, 5.8 Hz, 1 H), 2.46 (s, 3 H), 1.75 (s, 3 H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ 193.9 (C), 165.6 (C), 146.5 (CH), 146.4 (C), 134.0 (C), 130.0 (CH × 2), 129.9 (CH × 2), 129.8 (CH), 80.1 (C), 67.1 (CH), 42.7 (CH), 36.7 (CH_2), 23.9 (CH_3), 22.0 (CH_3); **HRMS** (ESI+) 343.0611 calcd for $C_{16}H_{16}O_5SNa$, found 343.0604.

(3*S*,3a*R*,7a*R*)-*tert*-Butyl-2,5-dioxo-7a-phenyl-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carboxylate (9b)

Using general method 2, **4b** cyclized in 3 h to give **9b** in 72% yield after flash-column chromatography (5 : 1 hexanes–EtOAc). Chiral-phase HPLC analysis (Chiralcel OD-H, 10% isopropanol in hexanes, 1 mL min^{-1}, λ = 225 nm) showed 78 : 22 er (RT_{minor} = 9.6 min, RT_{major} = 10.3 min). Using general method 1, racemic **9b** was obtained in 95% yield. **IR** (thin film) 2976, 2930, 1786, 1727, 1688, 1370, 1293, 1144, 989, 767, 700 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.47–7.44 (m, 5 H), 6.81 (dd, J = 10.3 Hz, 1 H), 6.37 (d, J = 10.3 Hz, 1 H), 3.47–3.45 (m, 2 H), 2.78–2.71 (m, 1 H), 2.61 (d, J = 17.7 Hz, 1 H), 1.50 (s, 9 H). Note: An additional singlet observed at 1.58 ppm was ascribed to residual water. **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ 194.8 (C), 169.4 (C), 165.3 (C), 144.8 (CH), 137.3 (C), 130.9 (CH), 129.5 (CH), 129.4 (CH × 2), 125.2 (CH × 2), 84.0 (C), 83.2 (C), 52.9 (CH), 46.9 (CH), 35.6 (CH_2), 28.1 (CH_3 × 3); **HRMS** (ESI+) 351.1203 calcd for $C_{19}H_{20}O_5Na$, found 351.1217.

(3*S*,3a*R*,7a*R*)-*tert*-Butyl-7a-isopropyl-2,5-dioxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carboxylate (9c)

Using general method 2, **4c** cyclized in 3 h to give **9c** in 77% yield after flash-column chromatography (3 : 1 hexanes–EtOAc). Chiral-phase HPLC analysis (Chiralcel OD-H, 10% isopropanol in hexanes, 1 mL min^{-1}, λ = 225 nm) showed 80 : 20 er (RT_{minor} = 7.7 min, RT_{major} = 8.2 min). Using general method 1, racemic **9c** was obtained in 96% yield. **IR** (thin film) 2976, 2937, 2884, 1784, 1730, 1688, 1470, 1369, 1294, 1149, 980 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.70 (dd, J = 10.5, 1.9 Hz, 1 H), 6.21 (d, J = 10.5 Hz, 1 H), 3.43 (dddd, J = 12.0, 5.5, 1.9, 1.9 Hz, 1 H), 3.33 (d, J = 12.1 Hz, 1 H), 2.72 (dd, J = 18.3, 5.7, Hz, 1 H), 2.58 (d, J = 17.2 Hz, 1 H), 2.25 (hept. J = 6.9 Hz, 1 H), 1.49 (s, 9 H), 1.11 (d, J = 6.9 Hz), 3 H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ 194.9 (C), 169.3 (C), 165.6 (C), 145.6 (CH), 131.1 (CH), 84.7 (C), 83.8 (C), 53.6 (CH), 40.1 (CH), 37.4 (CH_2), 36.1 (CH), 28.1 (CH_3 × 3), 17.7 (CH_3), 16.8 (CH_3); **HRMS** (ESI+) 317.1359 calcd for $C_{16}H_{22}O_5Na$, found 317.1375.

(3*S*,3a*R*)-*tert*-Butyl-7a-(2-methoxy-2-oxoethyl)-2,5-dioxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carboxylate (9d)

Using general method 2, **4d** cyclized in 3 h to give **9d** in 44% yield after flash-column chromatography (3 : 1 hexanes–EtOAc). Chiral-phase HPLC analysis (Chiralcel OD-H, 10% isopropanol in hexanes, 1 mL min^{-1}, λ = 225 nm) showed 77 : 23 er (RT_{major} = 21.9 min, RT_{minor} = 27.4 min). Using general method 1, racemic **9d** was obtained in 53% yield. **IR** (thin film) 2979, 2926, 2884, 1783, 1724, 1679, 1431, 1364, 1298, 1253, 1131, 979 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.82 (dd, J = 10.4, 2.0 Hz, 1 H), 6.17 (d, J = 10.4 Hz, 1 H), 3.74 (s, 3 H), 3.58–3.68 (m, 1 H), 3.35(d, J = 12.2 Hz, 1 H), 3.05 (d, J = 15.5 Hz, 1 H), 2.99 (d, J = 15.5 Hz, 1 H), 2.84 (dd, J = 18.0, 5.8 Hz, 1 H), 2.62 (d, J = 17.0 Hz, 1 H), 1.50 (s, 9 H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ 194.5 (C), 168.6 (C), 168.3 (C), 165.0 (C), 144.5 (CH), 130.7 (CH), 84.1 (C), 79.2 (C), 52.6 (CH_3), 52.4 (CH), 42.7 (CH), 42.3 (CH_2) 36.1(CH_2), 28.1 (CH_3 × 3); **HRMS** (ESI+) 347.1101 calcd for $C_{16}H_{20}O_7Na$, found 347.1111.

(3*S*,3a*R*,7a*R*)-*tert*-Butyl-7a-neopentyl-2,5-dioxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carboxylate (9e)

Using general method 2, **4e** cyclized in 2.5 h to give **9e** in 52% yield after flash-column chromatography (9 : 1 → 5 : 1 hexanes–EtOAc). Chiral-phase HPLC analysis (Chiralcel OJ, 5% ethanol in hexanes, 1 mL min^{-1}, λ = 225 nm) showed 80 : 20 er (RT_{major} = 8.8 min, RT_{minor} = 9.8 min). Using general method 1, racemic **9e** was obtained in 58% yield. **IR** (thin film) 2957, 1783, 1731, 1687, 1369, 1295, 1260, 1141, 983, 941 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.89 (d, J = 10.5 Hz, 1 H), 6.06 (d, J = 10.5 Hz, 1 H), 3.29 (s, 2 H), 2.74 (ddd, J = 17.9, 3.7, 1.4 Hz, 1 H), 2.61 (d, J = 18.2 Hz, 1 H), 2.04 (d, J = 15.2 Hz, 1 H), 1.93 (d, J = 15.2 Hz, 1 H), 1.49 (s, 9 H), 1.09 (s, 9 H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ 194.6 (C), 169.7 (C), 165.6 (C), 146.9 (CH), 128.7 (CH), 83.8 (C), 83.0 (C), 51.36 (CH), 51.30 (CH_2), 45.7 (CH), 35.7(CH_2), 31.5 (C), 31.4 (CH_3 × 3), 28.0 (CH_3 × 3); **HRMS** (ESI+) 345.1672 calcd for $C_{18}H_{26}O_5Na$, found 345.1677.

tert-Butyl-7a-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2,5-dioxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carboxylate (9f)

Using general method 2, **4f** cyclized in 22 h to give **9f** in 89% yield after flash-column chromatography (5 : 1 hexanes/EtOAc). Chiral-phase HPLC analysis (Chiralcel OD-H, 2% isopropanol in hexanes, 1 mL min^{-1}, λ = 225 nm) showed 75 : 25 er (RT_{major} = 11.8 min, RT_{minor} = 12.9 min). Using general method 1, racemic **9f** was obtained in 50% yield. **IR** (thin film) 2952, 2931, 2857, 1789, 1732, 1689, 1147, 1087, 838, 779 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.71 (dd, J = 10.4, 1.8 Hz, 1 H), 6.10 (d, J = 10.4 Hz), 3.91–3.79 (m, 2 H), 3.55 (dddd, J = 12.6, 5.6, 2.0, 2.0 Hz, 1 H), 3.34 (d, J = 12.4 Hz), 2.87 (dd, J = 17.9, 5.6 Hz, 1 H), 2.60 (d, J = 17.9 Hz, 1 H), 2.23 (ddd, J = 14.8, 7.1, 4.6 Hz, 1 H), 2.13 (ddd, J = 14.8, 6.1, 4.4 Hz, 1 H), 1.49 (s, 9 H), 0.88 (s, 9H), 0.07 (s, 6 H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ 195.1 (C), 169.5 (C), 165.4 (C), 146.7 (CH), 129.6 (CH), 83.6 (C), 82.0 (C), 57.9 (CH_2), 52.4 (CH), 43.0 (CH), 40.4 (CH_2), 36.1 (CH_2), 28.1 (CH_3 × 3), 25.9 (CH_3 × 3), 18.2 (C), −5.4 (CH_3 × 2); **HRMS** (ESI+) 433.2028 calcd for $C_{21}H_{34}O_6SiNa$, found 433.1996.

(3*S*,3a*R*,7a*R*)-*tert*-Butyl-7a-(2-methylpent-4-en-2-yl)-2,5-dioxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carboxylate (9g)

Using general method 2, **4g** cyclized in 19 h to give **9g** in 88% yield after flash-column chromatography (5 : 1 hexanes–EtOAc). Chiral-phase HPLC analysis (Chiralcel OJ, 3% isopropanol in hexanes, 1 mL min^{-1}, λ = 225 nm) showed 87 : 13 er. (RT_{major} = 16.1 min, RT_{minor} = 19.5 min). Using general method 1, racemic **9g** was obtained in 61% yield. **IR** (thin film) 2977, 2934, 1784, 1730, 1689, 1369, 1291, 1146, 982, 784 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ

6.83 (dd, J = 10.7, 2.0 Hz, 1 H), 6.24 (d, J = 10.6 Hz, 1 H), 5.81 (dddd, J = 17.4, 10.2, 7.3, 7.3 Hz, 1 H), 5.13 (d, J = 10.2, Hz, 1 H) 5.08 (d, J = 17.6 Hz, 1 H), 3.66 (dddd, J = 11.8, 6.1, 1.8, 1.8 Hz, 1 H), 3.31 (d, J = 11.9 Hz, 1 H), 2.75 (dd, J = 18.6, 6.1 Hz, 1 H), 2.57 (d, J = 18.1 Hz, 1 H), 2.32–2.18 (m, 2 H), 1.50 (s, 9 H), 1.10 (s, 3 H), 1.09 (s, 3 H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ 194.7 (C), 169.2 (C), 165.7 (C), 145.0 (CH), 133.3

(CH), 131.4 (CH), 119.2 (CH_2), 86.5 (C), 83.9 (C), 54.0 (CH), 41.7 (C), 41.5 (CH_2), 38.4 (CH), 37.9 (CH_2), 28.1 ($CH_3 \times 3$), 22.0 (CH_3), 21.8 (CH_3); **HRMS** (ESI+) 357.1672 calcd for $C_{19}H_{26}O_5Na$, found 357.1662.

(3*S*,3a*R*,4*R*,7a*S*)-*tert*-Butyl-4,6,7a- trimethyl-2,5-dioxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carboxylate (9h)

Using general method 2, **4h** cyclized in 36 h to give **9h** in 67% yield (isolated as a 12 : 1 mixture of diastereomers, measured by ^{1}H NMR) after flash-column chromatography (9 : 1→5 : 1 hexanes–EtOAc). Chiral-phase HPLC analysis (Chiralcel AS, 8% isopropanol in hexanes, 1 mL min^{-1}, λ = 225 nm) showed 69 : 31 er. RT_{minor} = 5.0 min (major diastereomer); 5.9 min (minor diastereomer) RT_{major} = 6.4 min (both diastereomers of the major enantiomer). Using general method 1, racemic **9h** was obtained in 74% yield. **IR** (thin film) 2991, 2987, 1785, 1736, 1690, 1451, 1371, 1283, 1148, 1078 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$, data for major diastereomer) δ 6.34 (dq, J = 1.6, 1.4 Hz, 1 H), 3.32 (ddd, J = 12.1, 5.0, 2.0 Hz, 1 H), 3.15 (d, J = 12.1 Hz, 1 H), 2.79 (qd, J = 6.9, 5.0 Hz, 1 H), 1.79 (d, J = 1.5 Hz, 1 H), 1.69 (s, 3 H), 1.46 (s, 9 H), 1.11 (d, J = 6.9 Hz, 3 H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT, data for major diastereomer) δ 197.9 (C), 170.3 (C), 166.7 (C), 141.2 (CH), 136.2 (C), 83.3 (C), 81.8 (C), 51.5 (CH), 51.4 (CH), 40.4 (CH), 27.8 ($CH_3 \times 3$), 24.1 (CH_3), 15.9 (CH_3), 12.9 (CH_3); **HRMS** (ESI+) 317.1359 calcd for $C_{16}H_{22}O_5Na$, found 317.1370; the NOE correlation used to assign the relative stereochemistry of **9h** is shown in Fig. 5.

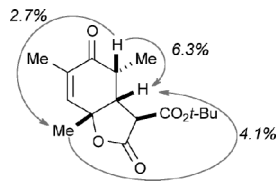


Fig. 5 NOE correlation for **9h**.

(3*S*,3a*R*,7a*S*)-*tert*-Butyl-7a-methyl-2,5-dioxo-6-(trimethylsilyl)-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carboxylate. (9i)

Using general method 2, **4i** cyclized in 4 d to give **9i** in 61% yield after flash-column chromatography (19 : 1 → 9 : 1 hexanes–EtOAc). Chiral-phase HPLC analysis (Chiralcel OD-H, 8% isopropanol in hexanes, 1 mL min^{-1}, λ = 225 nm) showed 65 : 35 er. (RT_{minor} = 4.7 min, RT_{major} = 5.1 min). Using general method 1, racemic **9i** was obtained in 49% yield. **IR** (thin film) 2984, 2927, 1779, 1730, 1655, 1340, 1297, 1248, 1145, 1096, 978, cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.71 (d, J = 1.2 Hz, 1 H), 3.26–3.25 (m, 2 H), 2.71 (ddd, J = 17.4, 3.9, 1.5 Hz, 1 H), 2.56 (dd, J = 17.5, 1.8 Hz, 1 H), 1.68 (s, 3 H), 1.49 (s, 9 H), 0.15 (s, 9 H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ 197.9 (C), 169.6 (C), 165.4 (C), 153.4 (CH), 142.8 (C), 83.8 (C), 80.6 (C), 52.5 (CH), 44.4 (CH), 36.7 (CH_2), 28.1 ($CH_3 \times 3$), 24.1 (CH_3), –1.5 ($CH_3 \times 3$); **HRMS** (ESI+) 361.1442 calcd for $C_{17}H_{26}O_5SiNa$, found 361.1437.

tert-Butyl-7-methoxy-6,7a-dimethyl-2,5-dioxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carboxylate (9j)

Using a modification of general method 1, in which 1.1 equiv. of Cs_2CO_3 was used, **4j** cyclized to give **9j** as a single regioisomer in 95% yield after flash-column chromatography (3 : 1 hexanes–EtOAc). **IR** (neat) 2978, 2928, 1784, 1732, 648, 1610, 1369, 1311, 1150 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.95 (s, 3 H), 3.35 (d, J = 12.4 Hz, 1 H), 3.21 (ddd, J = 12.4, 4.9, 2.9 Hz, 1 H), 2.73–2.59 (m, 2 H), 1.79 (s, 3 H), 1.77 (s, 3 H), 1.48 (s, 9 H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ 195.1 (C), 169.4 (C), 166.4 (C), 165.4 (C), 121.2 (C), 83.8 (C), 82.6 (C), 61.4 (CH_3), 52.0 (CH), 44.1 (CH), 35.7 (CH_2), 28.0 ($CH_3 \times 3$), 22.9 (CH_3), 9.2 (CH_3); **HRMS** (ESI+) 333.1309 calcd for $C_{16}H_{22}O_6Na$, found 333.1308.

(3a*R*,7a*S*)-*tert*-Butyl-6,7a-dimethyl-2,5-dioxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carboxylate (9k)

Using general method 1, **4k** gave **9k** and its regioisomer as a 9 : 1 inseparable mixture in 74% combined yield after flash-column chromatography (9 : 1 → 5 : 1 hexanes–EtOAc). **IR** (thin film) 2981, 2932, 1785, 1730, 1684, 1369, 1297, 1151, 1078, 983, 916, 840 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$, data for major regioisomer) δ 6.42 (s, 1 H), 3.31 (d, J = 12.3 Hz, 1 H), 3.27–3.20 (m, 1 H), 2.71 (dd, J = 17.7, 4.6 Hz, 1 H), 2.63 (dd, J = 17.6, 2.2 Hz, 1 H), 1.80 (d, J = 1.2 Hz, 3 H), 1.67 (s, 3 H), 1.48 (s, 9 H). Signals at δ 6.58 (dd, J = 10.3, 2.0 Hz) and δ 6.04 (d, J = 10.3 Hz) were ascribed to the minor regioisomer. **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT, data for major regioisomer) δ 195.0 (C), 169.6 (C), 169.5 (C), 142.3 (CH), 136.4 (C), 83.6 (C), 81.1 (C), 52.6 (CH), 44.7 (CH), 36.2 (CH_2), 28.0 ($CH_3 \times 3$), 24.2 (CH_3), 15.8 (CH_3); **HRMS** (ESI+) 303.1203 calcd for $C_{15}H_{20}O_5Na$, found 303.1213.

tert-Butyl-7,7a-dimethyl-2,5-dioxo-2,3,3a,4,5,7a-hexahydrobenzofuran-3-carboxylate (9l)

Using general method 1, **4l** gave **9l** and its regioisomer as a 12 : 1 inseparable mixture in 73% combined yield (3 : 1 hexanes–EtOAc). **IR** (neat) 2986, 2921, 1783, 1732, 1660, 1369, 1304, 1145, 1084 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.94 (dq, J = 1.2, 1.2 Hz, 1 H), 3.36 (d, J = 12.7 Hz, 1 H), 3.27 (ddd, J = 12.7, 5.2, 2.1 Hz, 1 H), 2.71 (dd, J = 18.0, 5.3 Hz, 1 H), 2.59 (ddd, J = 18.0, 2.1, 0.9 Hz, 1 H), 2.02 (d, J = 1.4 Hz, 3 H), 1.72 (s, 3 H), 1.48 (s, 9 H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ 194.2 (C), 169.4 (C), 165.5 (C), 157.9 (C), 127.9 (CH), 83.7 (C), 82.4 (C), 51.9 (CH), 45.4 (CH), 35.7 (CH_2), 28.0 ($CH_3 \times 3$), 23.0 (CH_3), 18.5 (CH_3); **HRMS** (ESI+) 303.1203 calcd for $C_{15}H_{20}O_5Na$, found 303.1204.

Cyclization of 4m

Using general method 1, **4m** cyclized to give **9a** (70% yield) and **9i** (8% yield) after flash-column chromatography (3 : 1 hexanes–EtOAc). Both products were identified by comparison of their spectroscopic data with that previously obtained.

tert-Butyl-5a-methyl-2,3-dioxo-2,2a,2a^1,2b,3,5a-hexahydrocyclopropa[_cd_]benzofuran-2a-carboxylate (12n)

Using a modification of general method 2, in which 1.0 equiv. of Cs_2CO_3 was used and the concentration was 0.1 M in substrate, **4n** cyclized to give **12n** in 45% yield after flash-column chromatography (2 : 1 hexanes–EtOAc). **IR** (thin film) 2979, 2932, 2856, 1784, 1726, 1685, 1370, 1315, 1137 cm $^{-1}$; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.87 (d, J = 9.8 Hz, 1 H), 6.18 (d, J = 9.8 Hz, 1 H), 3.18 (d, J = 7.5 Hz, 1 H), 3.02 (d, J = 7.5 Hz, 1 H), 1.80 (s, 3 H), 1.50 (s, 9 H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ 188.0 (C), 165.7 (C), 163.6 (C), 149.2 (CH), 131.6 (CH), 84.5 (C), 74.2 (C), 44.3 (C), 42.2 (CH), 35.6 (CH), 28.0 (CH_3 × 3), 25.6 (CH_3); **HRMS** (ESI+) 287.0890 calcd for $C_{14}H_{16}O_5Na$, found 287.0880.

(2a^1_R_,5a_S_)-_tert_-Butyl-5,5a-dimethyl-2,3-dioxo-2,2a,2a^1,2b,3,5a-hexahydrocyclopropa[_cd_]benzofuran-2a-carboxylate (12o)

Using general method 1, **4o** cyclized to give **12o** in >99% crude yield. Attempts to further purify crude **12o** by chromatography resulted in decomposition. **IR** (thin film) 2980, 2934, 1782, 1724, 1671, 1370, 1314, 1251, 1161, 1032, 919, cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.03 (app. t, J = 1.3 Hz, 3 H), 3.13 (d, J = 7.5 Hz, 1 H), 3.01 (dd, J = 7.5, 1.2 Hz, 1 H), 2.06 (d, J = 1.5 Hz, 3 H), 1.77 (s, 3 H), 1.51 (s, 9 H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ 187.9 (C), 165.8 (C), 163.7 (C), 159.2 (C), 129.1 (CH), 84.4 (C), 76.5 (C), 44.0 (C), 42.9 (CH), 36.1 (CH), 28.0 (CH_3 × 3), 23.3 (CH_3), 20.2 (CH_3); **HRMS** (ESI+) 301.1046 calcd for $C_{15}H_{18}O_5Na$, found 301.1052.

tert-Butyl-5-methoxy-4,5a-dimethyl-2,3-dioxo-2,2a,2a1,2b,3,5a-hexahydrocyclopropa[_cd_]benzofuran-2a-carboxylate (12p)

Using a modification of general method 1, in which 1.1 equiv. of Cs_2CO_3 was used, **4p** cyclized to give **12p** as a single regioisomer in 65% yield after flash column chromatography (3 : 1 hexanes–EtOAc). **IR** (neat) 2980, 2936, 1784, 1723, 1661, 1607, 1370, 1316, 1164, 1034 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.90 (s, 3 H), 3.08 (d, J = 7.7 Hz, 1 H), 3.02 (d, J = 7.7 Hz, 1 H), 1.86 (s, 3 H), 1.71 (s, 3 H), 1.49 (s, 9 H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ 189.3 (C), 170.4 (C), 166.0 (C), 163.4 (C), 120.5 (C), 84.2 (C), 78.3 (C), 61.6 (CH_3), 43.8 (C), 41.6 (CH), 35.4 (CH), 28.0 (CH_3 × 3), 22.1 (CH_3), 9.8 (CH_3); **HRMS** (ESI+) 331.1152 calcd for $C_{16}H_{20}O_6Na$, found 331.1158.

(2a1_R_,5a_S_)-_tert_-Butyl 4-bromo-5a-methyl-2,3-dioxo-2,2a,2a1,2b,3,5a-hexahydrocyclopropa[_cd_]benzofuran-2a-carboxylate (12q)

Using general method 2, **4q** cyclized in 5.5 h to give **12q** in 56% yield after flash-column chromatography (4 : 1 hexanes–EtOAc). Chiral-phase HPLC analysis (Chiralcel OD-H, 10% isopropanol in hexanes, 1 mL min^{-1}, λ = 225 nm) showed 83 : 17 er (RT_{major} = 13.1 min, RT_{minor} = 16.6 min). Using a modification of general method 1, in which CH_2Cl_2 was used as solvent and 10 mol% tetrabutylammonium iodide was added, racemic **12q** was obtained in 85%. **IR** (thin film) 3055, 2980, 2929, 1786, 1723, 1692, 1602, 1454, 1326, 1154, 1036, 917 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 (s, 1 H), 3.25 (d, J = 7.5 Hz, 1 H), 3.18 (d, J = 7.5 Hz, 1 H) 1.81 (s, 3 H), 1.51 (s, 9 H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ 181.6 (C), 165.0 (C), 163.0 (C), 149.3 (CH), 128.5 (C), 84.9 (C), 76.3 (C), 44.8 (C), 42.3 (CH), 35.4 (CH), 28.0 (CH_3 × 3), 25.9 (CH_3); **HRMS** (ESI+) 342.0097 calcd for $C_{14}H_{15}BrO_5$, found 341.9251.

(2a1_R_,5a_S_)-_tert_-Butyl-4-bromo-5a-isopropyl-2,3-dioxo-2,2a,2a1,2b,3,5a-hexahydrocyclopropa[_cd_]benzofuran-2a-carboxylate (12r)

Using general method 2, **4r** cyclized in 3.5 h to give **12r** in 81% yield after flash-column chromatography (5 : 1 hexanes–EtOAc). Chiral-phase HPLC analysis (Chiralcel OD-H, 10% isopropanol in hexanes, 1 mL min^{-1}, λ = 225 nm) showed 91 : 9 er. (RT_{major} = 8.3 min, RT_{minor} = 11.9 min). Using general method 1, racemic **12r** was obtained in 49% yield. **IR** (thin film) 3060, 2977, 1788, 1693, 1608, 1465, 1324, 1153, 1080, 955 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 (s, 1 H), 3.20 (d, J = 7.9 Hz, 1 H), 3.17 (d, J = 7.7 Hz, 1 H), 2.27 (qq, J = 6.8, 6.8 Hz, 1 H), 1.50 (s, 9 H), 1.10 (d, J = 6.9 Hz, 3 H), 1.09 (d, J = 6.8 Hz, 3 H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ 182.0 (C), 165.4 (C), 163.0 (C), 147.8 (CH), 129.3 (C), 84.7 (C), 81.7 (C), 44.6 (C), 38.5 (CH), 34.6 (CH), 34.3 (CH), 28.0 (CH_3 × 3), 16.1 (CH_3), 15.6 (CH_3); **HRMS** (ESI+) 370.0410 calcd for $C_{16}H_{19}BrO_5$, found 370.0141.

(2a1R,5aS)-_tert_-Butyl-4-bromo-5a-(2-methylpent-4-en-2-yl)-2,3-dioxo-2,2a,2a1,2b,3,5a-hexahydrocyclopropa[_cd_]benzofuran-2a-carboxylate (12s)

Using general method 2, **4s** cyclized in 6.5 d to give **12s** in 63% yield after flash-column chromatography (9 : 1 hexanes–EtOAc). Chiral-phase HPLC analysis (Chiralcel OD, 10% isopropanol in hexanes, 1 mL min^{-1}, λ = 225 nm) showed 72 : 23 er. (RT_{major} = 6.4 min, RT_{minor} = 10.0 min). Using general method 1, racemic **12s** was obtained in 42% yield. **IR** (thin film) 2976, 1786, 1728, 1694, 1314, 1261, 1150, 1092, 990, 837 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.54 (s, 1 H), 5.83 (ddt, J = 17.4, 10.1, 7.4 Hz, 1 H), 5.17 (dd, J = 10.1, 1.0 Hz, 1 H), 5.12 (dd, J = 17.4, 1.5 Hz, 1 H), 3.31 (d, J = 7.7 Hz, 1 H), 3.16 (d, J = 7.7 Hz, 1 H), 2.22 (d, J = 7.4 Hz, 2 H), 1.51 (s, 9 H), 1.11j (s, 3 H), 1.09 (s, 3 H); **^{13}C NMR** (75 MHz, $CDCl_3$, DEPT) δ 181.9 (C), 165.4 (C), 163.0 (C), 146.3 (CH), 132.8 (CH), 129.6 (C), 119.5 (CH_2), 84.8 (C), 83.7 (C), 44.7 (C), 40.7 (CH_2), 39.2 (C), 39.1 (CH), 34.3 (CH), 28.0 (CH_3 × 3), 21.0 (CH_3), 20.6 (CH_3); **HRMS** (ESI+) 433.0621 calcd for $C_{19}H_{23}O_5BrNa$, found 433.0556.

tert-Butyl-4-bromo-5a-(2-((_tert_-butyldimethylsilyl)oxy)ethyl)-2,3-dioxo-2,2a,2a^1,2b,3,5a-hexahydrocyclopropa[_cd_]benzofuran-2a-carboxylate (12t)

Using general method 2, **4t** cyclized in 22 h to give **12t** in 35% yield after flash-column chromatography (9 : 1 hexanes–EtOAc). Chiral-phase HPLC analysis (Chiralcel OD, 10% isopropanol in hexanes, 1 mL min^{-1}, λ = 225 nm) showed 79 : 21 er. (RT_{major} = 6.4 min, RT_{minor} = 10.0 min). Using general method 1, racemic **12t** was obtained in 24% yield. IR (thin film) 2952, 2930, 2857, 1792, 1726, 1694, 1152, 837 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 1 H), 3.98–3.89 (m, 2 H), 3.59 (d, 7.5 Hz), 3.18 (d, 7.5 Hz), 2.33–2.18 (m, 2 H), 1.51 (s, 9 H), 0.90 (s, 9 H), 0.084 (s, 3 H), 0.078 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 181.8 (C), 165.2 (C), 163.0 (C), 149.2 (CH), 127.9 (C), 84.7 (C), 78.3 (C), 57.9 (CH_2), 44.4 (C), 41.4 (CH), 40.2 (CH_2), 35.4 (CH), 28.0 (CH_3 × 3), 26.0 (CH_3 × 3), 18.3 (C), −5.4 (CH_3 × 2); HRMS (ESI+) 509.0965 calcd for $C_{21}H_{31}BrO_6SiNa$, found 509.0965.

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