JOC Article

1,2-Dioxines as Masked Cis γ-Hydroxy Enones and Their Versatility in the Synthesis of Highly Substituted γ-Lactones

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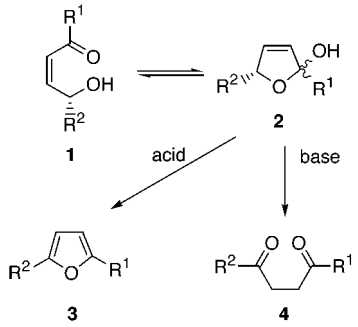
Addition of highly stabilized ester nucleophiles to 1,2-dioxines affords good to high yields of γ-lactones with high diastereoselectivity. Heterolytic or homolytic cleavage of the 1,2-dioxines under appropriate conditions generates the key reactive cis γ-hydroxy enones, which ultimately afford the observed γ-lactones. Diastereoselectivity is installed as a result of anti 1,4-addition by the ester enolate to the cis enones followed by intramolecular cyclization. The reaction is tolerant of a range of substitution patterns on the 1,2-dioxine while a broad range of esters are also accommodated. In addition to the synthesis of racemic γ-lactones, highly enantioenriched γ-lactones can also be synthesized when chiral cobalt(II) catalysts are employed for the initial homolytic ring-opening of the 1,2-dioxine.

Introduction

Cis γ-hydroxy enones **1** have found little reported use in synthetic organic chemistry, with the majority of their synthetic utility being centered on furan or 1,4-diketone formation. Furans **3** result when the reaction medium is acidic due to facile dehydration of the isomeric cis/trans hemiacetals **2**.[1−4] Conversely, under basic conditions the hemiacetals can undergo a Kornblum−Del La Mare rearrangement to yield the diketone, **4** (Scheme 1).[5] Cis γ-hydroxy enones have been synthesized from their trans γ-hydroxy enone isomers, via thermal or photolytic isomerization, but reaction yields have been poor due to competing acid-catalyzed furanisation.[6] This acid/base sensitivity has therefore limited not only their synthetic utility but also their synthesis.

1,2-Dioxines of the type shown, **6**, represent a class of compounds that are readily ring-opened homolytically or heterolytically, to yield cis γ-hydroxy enones **1**.[7−10] The dioxines are readily synthesized from their precursor dienes, **5**, by photooxidation using oxygen and a suitable photosensitizer.[7,11−13] Heterolytic ring-opening of the dioxine can be achieved under basic conditions utilizing mild amine base catalysis.[7,14] Alternatively, homolytic ring-opening of the 1,2-dioxines has been realized via the use of transition metals. Ruthenium(II) has been shown to ring-open 1,2-dioxines to give epoxides from both

SCHEME 1



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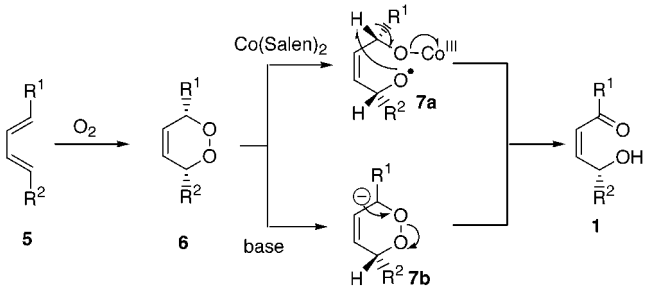
SCHEME 2



bicyclic and monocyclic 1,2-dioxines.[9] Similarly, palladium(0) has been shown to afford epoxides as well as cis γ-hydroxy enones; however, the cis γ-hydroxy enones rapidly decomposed to give furan.[8,15] O'Shea et al. have also utilized cobalt(II) complexes to rearrange 1,2-dioxines to yield cis γ-hydroxy enones which once again rapidly rearranged by the previously discussed mechanism to yield furan (Scheme 2).[10]

It is apparent within the literature that the reactivity of the cis γ-hydroxy enone functionality has precluded it from being a viable synthetic tool. 1,2-Dioxines[16] can be visualized as masked cis γ-hydroxy enones, since they may be efficiently converted to the enone via base or transition metal induced ring-opening. However, control of the ring-opening reaction, so that the cis γ-hydroxy enone does not further rearrange by the aforementioned processes, has been difficult to achieve due to the enones acid and base sensitivity.

Recently our research group has developed a variety of methods for the large-scale generation of these reactive cis enones from their precursor 1,2-dioxines under suitably mild conditions. In particular, we have explored the mild basicity of phosphorus ylides to effect the rearrangement of the 1,2-dioxines to the cis enones which then ultimately led to di- and trisubstituted cyclopropanes in a highly diastereoselective manner.[17a−e,g] This process has also been successfully applied to 1,2-dioxines that have been ring-opened by Co(II) catalysis.[17a−d] The reaction has been shown to proceed via the reactive cis γ-hydroxy enone, **1**, which undergoes facile syn 1,4-addition with respect to the hydroxyl moiety, in the presence of the ylide[17b−d] or phosphonate[17a] nucleophile to yield the desired cyclopropane. The facile nature of the syn 1,4-addition to the cis enone is thought to be due to the conformation of the cis enone, which can be held together by an internal hydrogen bond between the carbonyl and hydroxyl moieties.[4] This led us to suggest that other nucleophiles may undergo similar 1,4-additions to the enones and in essence trap the enone before it can further rearrange to the furan **3** or 1,4-diketone **4**. This paper describes the use of a broad range of 1,2-dioxines as masked cis γ-hydroxy enones and their conversion to highly substituted γ-lactones in both racemic and enantiomeric forms.[18−20]

SCHEME 3

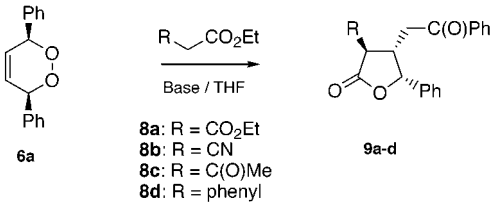


TABLE 1. Synthesis of Lactones 9a−d, Utilizing 1,2-Dioxine 6a and Esters 8a−d[a]

entry	R	lactone	yield (%)
1	CO_2Et	**9a**	93
2	CN	**9b**	93
3[b]	C(O)Me	**9c**	45
4[c]			70
5	Ph	**9d**	–
6[d]			–
7[e]			–

[a] General reaction conditions contained in experimental. [b] 1 equiv of ester. [c] 2 equiv of ester. [d] LiHMDS used as the base. [e] Prior rearrangement of dioxine with $Co(Salen)_2$.

Results and Discussion

The initial investigations centered on the use of β-stabilized enolate esters such as the enolate of diethyl malonate, with the 3,6-diphenyl dioxine **6a** chosen as the model 1,2-dioxine. The results are summarized below in Scheme 3 and Table 1.

The enolates of the disubstituted esters **8a−c** were allowed to react with dioxine **6a** affording the lactones **9a−c** in excellent yield. However, 2 equiv of ester **8c** was required to generate the lactone **9c** in high yield (entry 4). Monoester **8d** failed to react with dioxine **6a**, when employing either sodium ethoxide (entry 5) or LiHMDS (entry 6) as the base. In an attempt to get the enolate of **8d** to react, the 1,2-dioxine **6a** was rearranged to the cis γ-hydroxy enone by the addition of $Co(salen)_2$.[10,17b,c] Subsequent addition of the enolate of **8d** to the rearranged 1,2-dioxine, however, failed to afford the desired

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lactone (entry 7). In all cases where lactone was not the product (entries 5−7) the major product was the isomeric 1,4-diketone of the cis γ-hydroxy enone. This indicates that the resultant nucleophile, which derives from ester **8d**, is too basic and instead of adding in a anti 1,4-manner with respect to the R^2 grouping, simply rearranges the cis γ-hydroxy enone to the diketone via the Kornblum−Del La Mare mechanism previously discussed, a result that mirrors that found for the cyclopropanation reaction.[17b,c]

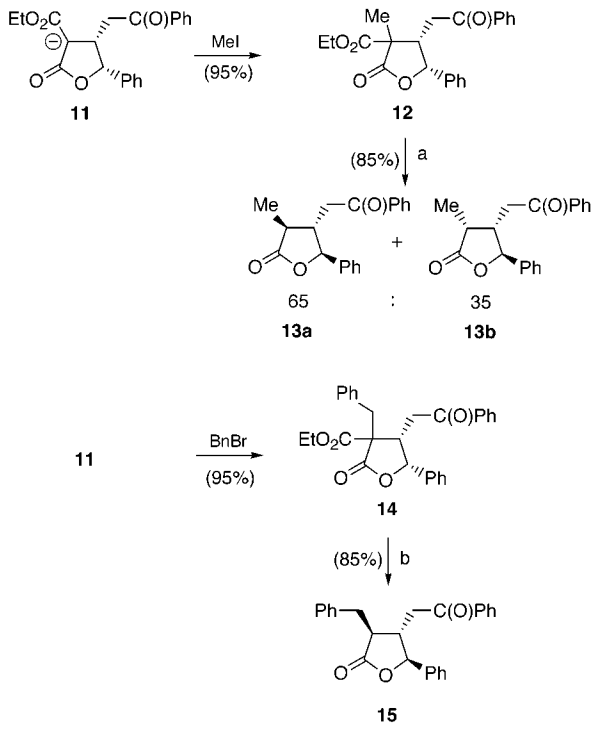
Each reaction was highly diastereoselective with the stereochemistry about the lactone ring system determined by 2-D ^{1}H and ^{13}C NMR techniques and further confirmed by a single-crystal analysis of **9c** (Supporting Information), and the acid **10**, derived from **9a**.[21,22] A small amount of a minor lactone isomer (≤5%) could be seen by ^{1}H NMR, but attempts to isolate this minor isomer were unsuccessful. It must be noted, however, that when the pure major isomer was allowed to stand in *d*-chloroform solution, small amounts of this minor isomer could be seen to appear over a period of days. This is due to the ready epimerization of the proton at the C_3 malonate center.

Each reaction required acidic workup due to the acidity of the C_3 proton and this therefore allowed for alkylation at this position prior to workup. Hence the anion of **11** was readily alkylated by the addition of MeI to give a mixture lactones, **12**, epimeric at C_3. Acidic decarboxylation of **12** gave lactones **13a** and **13b** epimeric at C_3. However, the relative stereochemistry at C_4 and C_5 had inverted, with an anti relationship now existing. Similarly, **11** was alkylated with BnBr to give lactone **14** which, after basic hydrolysis (with inversion) followed by decarboxylation, gave trisubstituted lactone **15** in an overall yield of 80% (Scheme 4).

Once again the stereochemistry at C_5 had inverted, giving an anti relationship between C_4 and C_5. This result can be explained by an intramolecular 'attack' from the carboxyl group during the decarboxylation step, via the intermediate **16a** to generate the more stable lactone **16b** (Scheme 5). The decarboxylation and inversion sequence is clearly a result of acid catalysis at elevated temperatures, as we had previously shown that no inversion or decarboxylation occurs during basic hydrolysis of the ester moiety at ambient temperature as confirmed by X-ray analysis of lactone **10**. The driving force of such an inversion is the relief of ring strain, thus yielding the more thermodynamically stable lactone, with the observed anti relationship at C_4 and C_5.[18]

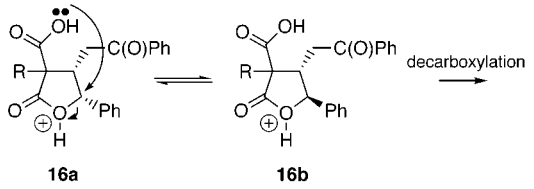
Proposed Mechanism. The mechanism of the reaction is thought to be related to that of the cyclopropanation reaction (Scheme 6).[17a−e] Initially, the ester anion removes the most acidic proton of the 1,2-dioxine, which then subsequently rearranges to the cis γ-hydroxy enone **1**. The enone then undergoes facile anti 1,4-addition by the ester nucleophile on the less hindered face of the enone, as determined by R^2. This intermediate **18** then undergoes a proton transfer, and the subsequent alkoxy intermediate **19** cyclizes to lactone **20**. The latter lactone exists as the anion until quenched with acid or an electrophile. The major isomer **21** results from protonation on the more hindered face and presumably represents a thermodynamic preference away from the all-cis isomer **22**. The small amounts of the other diastereomer, **22**, detected by ^{1}H NMR, presumably result from quenching of intermediate **20** from the less hindered face.

SCHEME 4[a]



[a] (a) 50% AcOH, reflux, 16 h; (b) (i) KOH (2 M), EtOH, (ii) toluene, reflux.

SCHEME 5

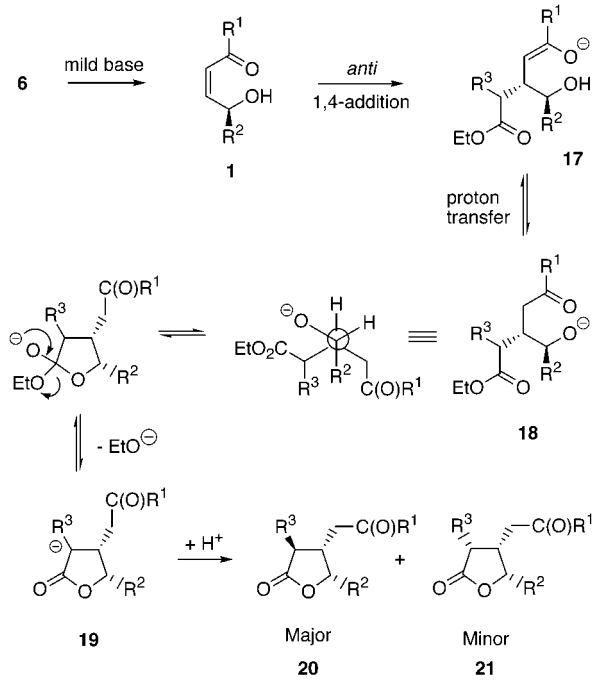


Scope of the Reaction. To highlight the potential of this process, ester nucleophiles **8a−c** were allowed to react with a range of monocyclic and bicyclic 1,2-dioxines to test the scope of the reaction. The results are summarized below in Table 2.

Yields were good to excellent for all of the lactones, and the diastereoselectivity for the lactones was also excellent, de 80−90%. As described previously, 2 equiv of ethyl acetoacetate were required for complete conversion of the 1,2-dioxines to lactones **22c** and **23c** (entries 3 and 6). The 3-substituted cyano lactones, **22b** and **23b** were also obtained in high yield; however, each lactone rapidly decomposed upon standing. Dialkyl dioxine, **6d**, required a reaction time of 5 days for conversion to the lactone **24**, and this reflects the reduced basicity of the α-protons of the 1,2-dioxine as compared to 1,2-dioxine **6a** (entry 7). As well as monocyclic 1,2-dioxines, bicyclic dioxine **6e** gave an excellent yield of the trans fused lactone **25a** (entry 8) as confirmed by 2-D ^{1}H and ^{13}C

(21) See Supporting Information for the X-ray data of **9c**.
(22) Greatrex, B. W.; Kimber, M. C.; Taylor, D. K.; Fallon, G. *Acta Crystallogr. E58*, **2002**, o298−o299.

SCHEME 6



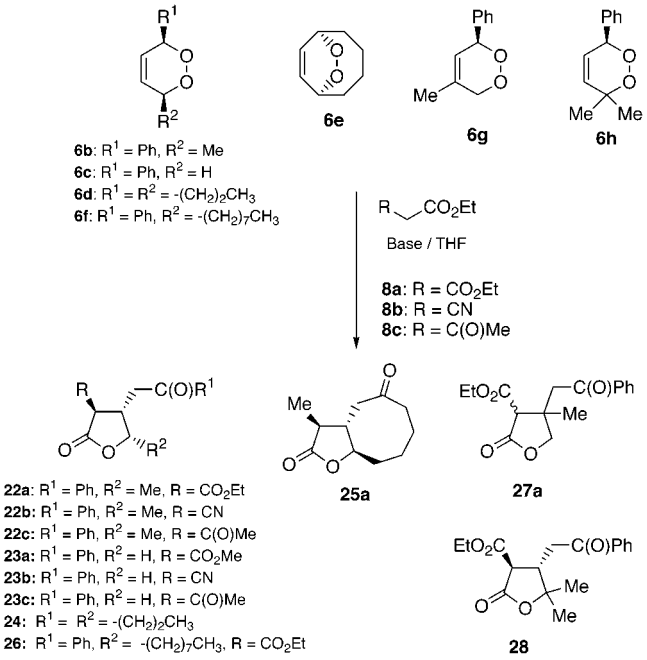
NMR techniques and X-ray analysis of the parent acid, **25b**.[23] The trans stereochemistry of **25** arises from the 1,4-addition of the malonate anion to the cis enone, with addition now being directed by the hydroxyl group, due to the conformation of the cyclooctyl ring system (Scheme 7).

Additionally, long alkyl-chained dioxine **6f** was tolerant of the reaction conditions as seen in entry 9. 3,5-Disubstituted dioxine **6g** gave a high yield of the lactone **27a** as a 1:1 mixture, epimeric at C_3 (entry 10). 3,3-Dimethyl dioxine **6h** also gave the desired lactone **28** in excellent yield and de (entry 11). The results shown in Table 2 indicate that this reaction is general for a range of 1,2-dioxines and could conceivably be applied to many other novel 1,2-dioxines.

Optically Enriched Lactones. It has been previously shown that 1,2-dioxines can be rearranged by cobalt(II) to afford cis γ-hydroxy enones in high yield.[17a−d] Additionally, when chiral cobalt(II) complexes are used to rearrange the dioxines, optically active enones result.[24] Hence, it was a logical progression to utilize this process to generate optically active lactones. When dioxine **6a** was allowed to react with optically pure cobalt(II) catalysts (**29** and **30a**,**b**),[25] optically enriched enone was formed which was converted to the subsequent lactones **31**, **32**, and **33** when treated with the anions of **6a**−**c** (Scheme 8 and Table 3).[26]

Yields for each transformation were good to excellent (65−95%) and the ee introduced into each lactone was also high (77−82%). Bornoxy Co(II) catalyst **29** introduced similar ee's into each lactone, irrespective of which ester nucleophile was utilized (entries 1−3). Menthoxy

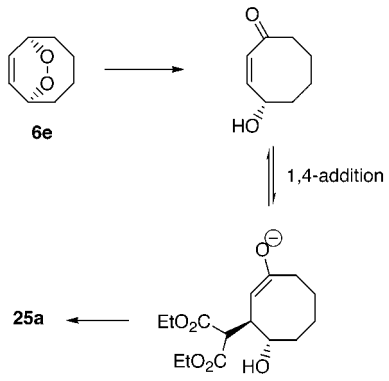
TABLE 2. Reaction of Diester Nucleophiles 8a−c with a Range of 1,2-Dioxines[a]



entry	1,2-dioxine	nucleophile	lactone	yield (%)
1	**6b**	**8a**	**22a**	97
2	**6b**	**8b**	**22b**	78
3[b]	**6b**	**8c**	**22c**	85
4	**6c**	**8a**	**23a**	92
5	**6c**	**8b**	**23b**	65
6[b]	**6c**	**8c**	**23c**	74
7[c]	**6d**	**8a**	**24**	56
8	**6e**	**8a**	**25a**	65
9	**6f**	**8a**	**26**	93
10[d]	**6g**	**8a**	**27a**	84
11	**6h**	**8a**	**28**	95

[a] General reaction conditions contained in experimental. [b]2 equiv of **8c** used. [c]Reaction time of 5 days required for complete consumption of **6d**. [d]**27a** isolated as a 1:1 mixture, epimeric at C_3, and was fully characterized as the decarboxylated product **27b**.

SCHEME 7



(23) Greatrex, B. W.; Kimber, M. C.; Taylor, D. K.; Fallon, G. *Acta Crystallogr.*, E58, **2002**, o248−o249.

(24) Avery, T. A.; Jenkins, N. F.; Kimber, M. C.; Lupton, D. W.; Taylor, D. K. *J. Chem. Soc., Chem. Commun.* **2002**, 28.

(25) For general methods on the synthesis of β-ketoiminato ligands and Co(II) complexes, see: Sugi, K. D.; Nagata, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1997**, 493. Nagata, T.; Imagawa, K.; Yamada, T. *Inorg. Chim. Acta* **1994**, *220*, 283. Nagata, T.; Imagawa, K.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1994**, 1259. Mukaiyama, T.; Yamada, T.; Nagata, T.; Imagawa, K. *Chem. Lett.* **1993**, 327.

(26) While the use of asymmetric cobalt(II) catalysis is currently limited to symmetrical meso 1,2-dioxines, we are currently exploring this methodology using unsymmetrical 1,2-dioxines, and this will be reported on in due course.

SCHEME 8

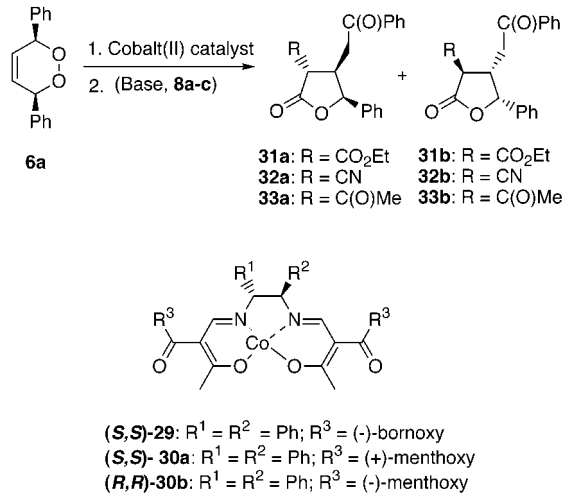


TABLE 3. Formation of Optically Enriched Lactones 31−33 Using Chiral Co(II) Catalysts 29, 30a, and 30b and Meso 1,2-Dioxine 6a[a]

entry	lactone	ratio of **a**:**b**	ee[b]
1	**31**	10:90	80
2[c]	**32**	–	–
3	**33**	9:91	82
4[d]	**31**	11.5:88.5	77
5[e]		89:11	78

[a] See experimental for reaction conditions. Reaction carried out using chiral Co(II) catalyst **29** unless otherwise stated. [b]ee determined by ^{1}H NMR and chiral shift reagent. [c]ee could not be determined due to insolubility of **32** in chiral shift solvent. [d]Reaction carried out using chiral Co(II) catalyst **30a**. [e]Reaction carried out using chiral Co(II) catalyst **30b**.

catalysts **30a** and **30b** (entries 4 and 5) generated enantio-enriched lactones of opposite absolute configuration. These results therefore suggest that the ee is being introduced into the cis γ-hydroxy enone, before the anti 1,4-addition of the ester nucleophiles.[27] Absolute configuration of the lactones was established by X-ray crystallographic analysis of the enantiopure lactone **35**[28,29] which was synthesized by the method shown in Scheme 9 and is depicted in the Supporting Information.

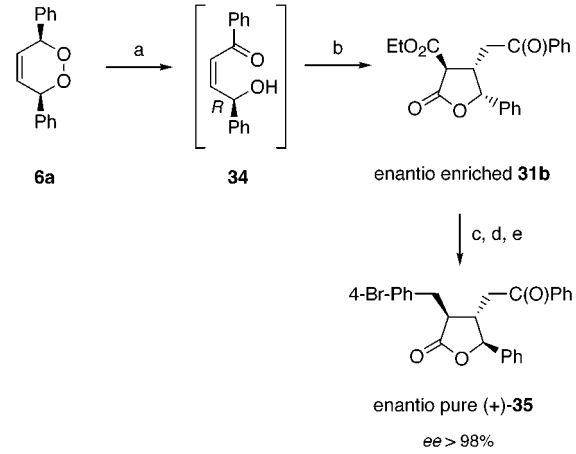
The absolute configuration of lactone **35** implies that the stereochemistry of the cis γ-hydroxy enone derived from the action of **29** on **6a**, after the 1,4-addition, is that shown in structure **34**. Additionally, it can be deduced, from the results shown in Table 3, that catalyst **30a** generates a cis γ-hydroxy enone with the configuration shown in structure **34**, while catalyst **30b** generates a cis γ-hydroxy enone with opposite absolute configuration. A full disclosure of the mechanism for introduction of ee into the cis γ-hydroxy enone, by the action of chiral cobalt(II) complexes on meso 1,2-dioxines, will be described shortly.

(27) This result is in agreement with that found for the cyclopropanation process. Full details on the mechanism of chiral Co(II) ring-opening of the 1,2-dioxine and the mode of induction of ee into the cis γ-hydroxy enone is currently being investigated and will be reported on in due course.

(28) The enantio-purity of **35** was established by chiral shift ^{1}H NMR and was shown to be >98%.

(29) See Supporting Information for X-ray data of **35**.

SCHEME 9[a]



[a] (a) Cobalt(II) catalyst **29**, THF, −4 °C; (b) diethyl malonate, EtONa, 16 h, rt; (c) (i) EtONa (1 equiv), THF, (ii) 4-bromobenzyl bromide (1 equiv); (d) (i) KOH (2 M), EtOH, (ii) toluene, reflux; (e) recrystallized (×3).

Conclusions

The methodology described herein has shown cis γ-hydroxy enones to be useful synthetic precursors for the synthesis of γ-lactones and that the functionality of the 1,2-dioxine presents itself as a viable masking group for the reactive cis enone. The synthesis of the γ-lactones is limited to the use of double stabilized esters since monostabilized esters appear to be too basic and thus rearrange the cis enone exclusively to the 1,4-diketone via a Kornblum−Del La Mare mechanism. γ-Lactones are an important class of compounds that form an integral part of a number of natural products and are vital synthetic intermediates in organic synthesis. Since 1,2-dioxines can be easily prepared from readily available dienes this methodology presents itself as a simple, yet efficient method to generate highly substituted γ-lactones in high yield and in high de. In addition, with the use of chiral Co(II) catalysts in the homolytic ring opening of 1,2-dioxines, this methodology can also be extended to the synthesis of enantio-enriched γ-lactones. We are currently utilizing this methodology in the synthesis of a number natural products, which will be reported on in due course.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were obtained on a 600, 300 or 200 MHz instrument using *d*-chloroform solutions as indicated. Optical rotation measurements were obtained on a PO1A AR21 polarimeter referenced to the sodium D line (589 nm) at 20 °C. Electron impact mass spectra (EI-MS) were recorded at 70 eV. Accurate mass measurements were performed at the Central Science Laboratory, University of Tasmania, Tasmania, Australia. Microanalyses were performed by the Department of Chemistry, University of Otago, Dunedin, New Zealand. Flash chromatography was conducted using Merck silica gel 60 of particle size 0.040−0.063 mm. Thin-layer chromatography (TLC) was performed on aluminum backed sheets of Merck silica gel 60F (254), which were visualized under 254 nm light or developed in vanillin dip. All organic extracts were dried with anhydrous sodium sulfate. Hexanes refers to the fraction boiling range 66−68 °C. Where necessary dichloromethane was distilled from phosphorus pentoxide and tetrahydrofuran was distilled from sodium−

benzophenone ketyl. The following compounds were prepared by standard literature methods: 3,6-diphenyl-3,6-dihydro-1,2-dioxine, **6a**;[13] 3-methyl-6-phenyl-3,6-dihydro-1,2-dioxine, **6b**;[13] 3-phenyl-3,6-dihydro-1,2-dioxine, **6c**;[13] 3,6-dipropyl-3,6-dihydro-1,2-dioxine, **6d**;[17b] 9,10-dioxabicyclo[4.2.2]decane, **6e**;[14,30] 4-methyl-6-phenyl-3,6-dihydro-1,2-dioxine, **6g**;[12] 3,3-dimethyl-6-phenyl-3,3-dihydro-1,2-dioxine, **6h**.[14]

3-Octyl-6-phenyl-3,6-dihydro-1,2-dioxine, 6f. 1-Phenyl-1,3-dodecadiene[31] (1.22 g, 5.03 mmol) was dissolved in dry dichloromethane (100 mL), rose bengal and bis(triethylammonium) salt (0.100 g) were added, the mixture was cooled to 4 °C, and a stream of O_2 was then passed through the solution. The reaction was then irradiated with a tungsten halogen lamp (500 W) at a distance of 10 cm for 6 h. After this period, the residual solvent was removed under reduced pressure and the residue chromatographed (1:1, dichloromethane:hexanes). This yielded the titled compound as a colorless oil (0.256 g, 19%). IR (oil) 1733, 1455, 1377, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26−1.79 (m, 17H), 4.54−4.58 (m, 1H), 5.49−5.51 (m, 1H), 6.04−6.14 (m, 2H), 7.33−7.40 (m, 5H). MS (M^+, %) 274 ($M^{\bullet+}$, 15), 242 (100), 143 (90), 129 (85), 105 (87), 77 (67), 57 (68), 43 (92). HRMS calcd for $C_{18}H_{26}O_2$, 274.1933; found, 274.1919.

General Lactonization Procedure Using Diethyl Malonate. To a solution of sodium ethoxide (0.5 M, 2.2 mL) and THF (4 mL) was added diethyl malonate, **8a** (1 mmol), and the reaction was stirred for 15 min under an N_2 atmosphere. To this solution was added the 1,2-dioxine (1 mmol), and the reaction was stirred for 16 h. After this period, the reaction was quenched by the addition of 1 M HCl (2 mL), and the mixture was partitioned between dichloromethane (50 mL) and 1 M HCl (50 mL). The aqueous layer was then extracted, the organic layers were dried and filtered, and the solvent was removed under reduced pressure. Column chromatography (60:40, hexane:ethyl acetate) yielded the following substituted lactones:

(±)-Ethyl 2-Oxo-4-(2-oxo-2-phenylethyl)-5-phenyltetrahydro-3-furancarboxylate, 9a. As a colorless oil (R_f 0.62, 60:40, hexanes:ethyl acetate). IR (oil): 2983, 1782, 1732, 1683, 1597, 1581, 1497, 1449, 1371, 1341 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.34 (t, J = 7.2 Hz, 3H), 2.63 (dd, J = 8.4, 18.3 Hz, 1H), 2.91 (dd, J = 6.0, 18.3 Hz, 1H), 3.54 (d, J = 9.6 Hz, 1H), 3.90 (dddd, J = 6.0, 7.5, 8.4, 9.6 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 6.04 (d, J = 7.5 Hz, 1H), 7.11−7.14 (m, 2H), 7.26−7.30 (m, 3H), 7.36−7.42 (m, 2H), 7.51−7.54 (m, 1H), 7.68−7.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 38.3, 39.9, 50.9, 62.3, 82.2, 125.7, 127.7, 128.4, 128.5, 128.7, 128.8, 133.4, 135.2, 167.1, 171.3, 197.3; MS (M^+, %) 353 ($M^{\bullet+}$, 20), 232 (72), 186 (32), 159 (26), 105 (100), 77 (52). Anal. Calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72%. Found C, 71.32, H, 5.81%.

(±)-2-Oxo-4-(2-oxo-2-phenylethyl)-5-phenyltetrahydro-3-furancarboxylic Acid, 10. Lactone **9a** (0.050 g, 0.142 mmol) was dissolved in ethanol (2 mL) and stirred overnight with 2 M KOH (2 mL). After this period, the solution was acidified, the aqueous layer extracted with dichloromethane (10 mL), the organic layer was dried and filtered, and the solvent was removed under reduced pressure. The residue was then crystallized from dichloromethane/hexanes to yield the acid as white plates (0.035 g, 76%). mp 130−132 °C decomp. IR (Nujol) 1783, 1711, 1678, 1457, 1377, 1336, 1300, 1267 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.67 (dd, J = 9.3, 18.6 Hz, 1H), 3.26 (dd, J = 5.1, 18.6 Hz, 1H), 3.64 (d, J = 10.8 Hz, 1H), 3.90 (dddd, J = 5.1, 7.8, 9.3, 10.8 Hz, 1H), 6.14 (d, J = 7.8 Hz, 1H), 7.12−7.14 (m, 2H), 7.31−7.36 (m, 3H), 7.42−7.44 (m, 2H), 7.51−7.57 (m, 1H), 7.74−7.77 (m, 2H); MS (M^+, %) 324 ($M^{\bullet+}$, 12), 280 (10), 252 (18), 174 (15), 146 (28), 120 (25), 105 (100), 77 (52). Anal. Calcd for $C_{19}H_{16}O_5$: C, 70.36; H, 4.97%. Found C, 70.31; H, 4.90%.

(±)-Ethyl 5-Methyl-2-oxo-4-(2-oxo-2-phenylethyl)-tetrahydro-3-furancarboxylate, 22a. As a clear oil (R_f 0.55, 60:40, hexanes:ethyl acetate). IR (oil) 2983, 1778, 1732, 1685, 1597, 1581, 1449, 1373, 1275 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (d, J = 6.6 Hz, 1H), 1.34 (t, J = 7.2 Hz, 3H), 3.14−3.31 (m, 2H), 3.40 (d, J = 9.9 Hz, 1H), 3.60 (m, 1H), 4.29 (q, J = 7.2 Hz, 2H), 5.14−5.17 (m, 1H), 7.46−7.52 (m, 2H), 7.58−7.64 (m, 1H), 7.93−7.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 15.8, 37.5, 38.5, 51.1, 62.2, 77.6, 127.9, 128.8, 133.7, 135.9, 167.2, 170.8, 196.9; MS (M^+, %) 290 ($M^{\bullet+}$,15), 245 (38), 226 (31), 200 (12), 105 (100), 77 (21). Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25%. Found C, 65.95, H, 6.22%.

(±)-Ethyl 2-Oxo-4-(2-oxo-2-phenylethyl)-tetrahydro-3-furancarboxylate, 23a. As white plates, mp 67.5−69.5 °C (R_f 0.42, 60:40, hexanes:ethyl acetate). IR (Nujol) 2984, 1778, 1731, 1684, 1596, 1449, 1372, 1225 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.31 (t, J = 7.1 Hz, 3H), 3.18 (dd, J = 8.4, 18.0 Hz, 1H), 3.39 (dd, J = 5.7, 18.0 Hz, 1H), 3.40 (d, J = 8.7 Hz, 1H), 3.53 (ddddd, J = 5.7, 7.8, 7.8, 8.4, 8.7 Hz, 1H), 4.01 (dd, J = 7.8, 9.0 Hz, 1H), 4.30 (q, J = 7.8 Hz, 2H), 4.81 (dd, J = 7.8, 9.0 Hz, 1H), 7.48−7.51 (m, 2H), 7.58−7.64 (m, 1H), 7.91−7.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 35.7, 40.9, 51.8, 62.3, 71.9, 128.0, 128.8, 131.4, 133.8, 167.2, 171.4, 197.8; MS (M^+, %) 277 ($M^{\bullet+}$, 100), 231 (10), 145 (63), 105 (22). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84%. Found C, 65.03; H, 5.90%.

(±)-Ethyl 2-Oxo-4-(2-oxopentyl)-5-propyltetrahydro-3-furancarboxylate, 24. As a colorless oil (R_f 0.44; 70:30, hexanes:ethyl acetate). IR (oil) 2963, 2876, 1780, 1737, 1714, 1374, 1262, 1157 cm-[1]; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, J = 7.5 Hz, 3H), 0.95 (t, J = 6.9 Hz, 3H), 1.20−1.44 (m, 6H), 1.55−1.64 (m, 3H), 2.41 (t, J = 7.2 Hz, 2H), 2.55−2.72 (m, 2H), 3.26 (d, J = 9.3 Hz, 1H), 3.35−3.41 (m, 1H), 4.26 (q, J = 7.2 Hz, 2H), 4.80−4.89 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.5, 13.6, 13.9, 17.1, 18.9, 32.3, 38.0, 41.1, 44.7, 51.7, 62.1, 81.1, 167.2, 170.9, 207.8; MS (M^+, %) 285 ($M^{\bullet+}$, 30), 199 (18), 153 (30), 71 (94), 43 (100). Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51%. Found C, 63.52; H, 8.66%.

(±)-Ethyl 2,5-Dioxoperhydrocycloocta[*b*]furan-3-carboxylate, 25a. As a colorless oil (R_f 0.54, 60:40, hexanes:ethyl acetate). IR (oil) 3545, 1786, 1736, 1459, 1374, 1337, 1273 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.32 (t, J = 7.2 Hz, 3H), 1.41−1.17 (m, 1H), 1.73−1.85 (m, 3H), 1.86−1.92 (m, 1H), 2.16−2.21 (m, 1H), 2.33 (dt, J = 5.4, 13.2 Hz, 1H), 2.41 (dd, J = 11.4, 14.4 Hz, 1H), 2.70 (dd, J = 3.6, 14.4 Hz, 1H), 2.71−2.76 (m, 1H), 3.14−3.21 (m, 1H), 3.35 (d, J = 12.0 Hz, 1H), 4.12−4.16 (m, 1H), 4.25−4.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.9, 22.0, 25.8, 31.0, 39.0, 43.9, 45.2, 53.7, 62.2, 83.9, 166.5, 169.3, 211.4; MS (M^+, %) 255 ($M^{\bullet+}$+ H, 100), 237 (10), 208 (25), 196 (32), 141 (18), 123 (30), 105 (52). Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.14%. Found: C, 61.64; H, 7.40%.

(±)-2,5-Dioxoperhydrocycloocta[b]furan-3-carboxylic Acid, 25b. Prepared using the same method as **10** (0.033 g, 74%). mp 128−130 °C, decomp. IR (Nujol) 1776, 1726, 1677, 1377, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.42−1.48 (m, 1H), 1.73−1.86 (m, 3H), 1.88−1.94 (m, 1H), 2.19−2.24 (m, 1H), 2.33−2.37 (m, 1H), 2.42−2.47 (dd, J = 12, 14.4 Hz, 1H), 2.73−2.78 (m, 1H), 3.01−3.04 (dd, J = 3.6, 14.4 Hz, 1H), 3.10−3.16 (m, 1H), 3.39 (d, J = 12.6 Hz, 1H), 4.18−4.21 (m, 1H); MS (M^+, %) 226 ($M^{\bullet+}$, 10), 208 (27), 153 (22), 125 (23), 124 (88), 95 (40), 68 (55), 41 (100). HRMS Calcd for $C_{11}H_{14}O_5$: 226.0841; found: 226.0849.

(±)-Ethyl 5-Octyl-2-oxo-4-(2-oxo-2-phenylethyl)-tetrahydro-3-furancarboxylate, 26. As a viscous oil (R_f 0.55, 60:40, hexanes:ethyl acetate). IR (oil) 1778, 1735, 1686, 1449, 1372, 1344, 1229 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (m, 3H), 1.17−2.04 (m, 17H), 3.21 (d, J = 7.2 Hz, 2H), 3.38 (d, J = 9.3 Hz, 1H), 3.58 (m, 1H), 4.22 (q, J = 7.2 Hz, 2H), 4.93−4.95 (m, 1H), 7.46−7.51 (m, 2H), 7.58−7.61 (m, 1H), 7.92−7.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 22.6, 25.7, 29.1, 29.2, 29.3, 30.3, 31.8, 37.3, 38.5, 51.8, 62.3, 81.6, 128.0, 128.8, 133.8, 135.9, 167.3, 171.4, 197.0 (two alkyl carbons are masked); MS (M^+, %) 389 ($M^{\bullet+}$, 21), 285 (62), 257 (18), 143 (86), 105 (100), 69 (64). Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30%. Found: C, 70.80; H, 8.01%.

(±)-Ethyl 4-Methyl-2-oxo-4-(2-oxo-2-phenylethyl)-tetrahydro-3-furancarboxylate, 27a. As a colorless oil (R_f 0.42, 70:30, hexanes:ethyl acetate). Obtained as a 1:1 mixture of

(30) Kayama, Y.; Oda, M.; Kitahara, Y. *Chem. Lett.* **1974**, 345.
(31) Liu, R. Q.; Shlosser, M. *Synlett* **1996**, *12*, 1195.

isomers, epimeric at C_3, which were assigned by 2-D ^{1}H NMR. (A) ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.24 (t, J = 7.2 Hz, 3H), 1.37 (s, 3H), 3.07 (d, J = 18.0 Hz, 1H), 3.46 (s, 1H), 3.47 (d, J = 18.0 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 4.33 (d, J = 9.0 Hz, 1H), 4.49 (d, J = 9.0 Hz, 1H), 7.43−7.48 (m, 2H), 7.55−7.59 (m, 1H), 7.87−7.89 (m, 2H); (B) ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.29 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 3.16 (d, J = 18.0 Hz, 1H), 3.47 (d, J = 18.0 Hz, 1H), 3.58 (s, 1H), 4.25 (q, J = 7.2 Hz, 2H), 4.32 (d, J = 9.0 Hz, 1H), 4.41 (d, J = 9.0 Hz, 1H), 7.43−7.48 (m, 2H), 7.55−7.59 (m, 1H), 7.91−7.92 (m, 2H); MS (M^+, %) 291 ($M^{\bullet+}$, 32), 245 (10), 159 (52), 120 (100), 105 (92), 77 (98). The mixture was not separated but decarboxylated as follows. The mixture was refluxed in 50% acetic acid solution (5 mL) for 16 h. After this period, the reaction was cooled and basified and the aqueous layer extracted with dichloromethane (50 mL). The combined organic extracts were then dried and filtered, and the solvent was removed under reduced pressure. This yielded **(±)-4-methyl-2-oxo-4-(2-oxo-2-phenylethyl)-tetrahydrofuran**, **27b**, as a white solid, which was purified by chromatography (R_f 0.48, 60:40, hexanes:ethyl acetate), mp 64.5−66 °C. IR (Nujol) 1760, 1681, 1454, 1419, 1372, 1307, 1291, 1194, 1167 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.34 (s, 3H), 2.48 (d, J = 17.4 Hz, 1H), 2.63 (d, J = 17.4 Hz, 1H), 3.13 (d, J = 17.4 Hz, 1H), 3.31 (d, J = 17.4 Hz, 1H), 4.26−4.33 (m, 2H), 7.45−7.51 (m, 2H), 7.57−7.61 (m, 1H), 7.91−7.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.1, 38.3, 42.1, 46.0, 78.3, 127.8, 128.7, 133.5, 136.8, 176.2, 197.4; MS (M^+, %) 219 ($M^{\bullet+}$, 92), 159 (33), 120 (100), 105 (34). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47%. Found: C, 71.81; H, 6.34%.

(±)-Ethyl 5-Dimethyl-2-oxo-4-(2-oxo-2-phenylethyl)-tetrahydro-3-furancarboxylate, 28. As a colorless oil that crystallized upon standing, mp 65−67 °C (R_f 0.48, 60:40. hexanes:ethyl acetate). IR (oil) 3533, 3062, 2981, 1772, 1687, 1449, 1377, 1352, 1267 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, J = 7.2 Hz, 3H), 1.30 (s, 3H), 1.48 (s, 3H), 3.10−3.17 (m, 2H), 3.21−3.30 (m, 1H), 3.43 (d, J = 11.4 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 7.40−7.45 (m, 2H), 7.53 (m, 1H), 7.87−7.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 22.8, 27.1, 37.9, 44.9, 53.1, 61.7, 85.3, 127.9, 128.6, 133.4, 135.9, 167.5, 170.3, 196.8; MS (M^+, %) 304 ($M^{\bullet+}$, 18), 259 (30), 240 (60), 105 (100). Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62%. Found: C, 67.20; H, 6.66%.

General Lactonization Procedure Using Ethyl Cyanoacetate. To a solution of sodium ethoxide (0.5 M, 2.2 mL, 1.1 mmol) and THF (4 mL) was added ethyl cyanoacetate, **6b** (1.05 mmol), and the reaction was stirred for 15 min under an N_2 atmosphere. To this solution was added the 1,2-dioxine (1.0 mmol), and the reaction was stirred for 16 h. After this period, the reaction was quenched by the addition of 1 M HCl (2 mL) and the mixture partitioned between dichloromethane (50 mL) and 1 M HCl (50 mL). The aqueous layer was then extracted and the subsequent organic layers dried, filtered and the solvent removed under reduced pressure. Column chromatography (60:40, hexanes:ethyl acetate) yielded the following substituted lactones:

(±)-2-Oxo-4-(2-oxo-2-phenylethyl)-5-phenyltetrahydro-3-furancarbonitrile, 9b. As a fine white crystals, mp 129−131 °C (R_f 0.54, 60:40, hexanes:ethyl acetate). IR (Nujol) 1774, 1675, 1369, 1340, 1322, 1282, 1182 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.00 (d, J = 6.9 Hz, 2H), 3.95 (ddd, J = 6.9, 6.9, 9.0 Hz, 1H), 4.16 (d, J = 9.0 Hz, 1H), 5.85 (d, J = 6.9 Hz, 1H), 7.21−7.32 (m, 5H), 7.37−7.41 (m, 2H), 7.50−7.56 (m, 1H), 7.67−7.69 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.1, 37.5, 38.3, 83.0, 113.3, 125.6, 125.8, 127.8, 128.5, 128.9, 129.2, 133.6, 135.8, 167.6, 196.1; MS (M^+, %) 306 ($M^{\bullet+}$, 32), 256 (10), 199 (22), 120 (48), 105 (100), 77 (32). Anal. Calcd for $C_{19}H_{15}N_1O_3$: C, 74.74; H, 4.95; N, 4.59%. Found C, 74.47; H, 4.91; N, 4.64%.

(±)-5-Methyl-2-oxo-4-(2-oxo-2-phenylethyl)-tetrahydro-3-furancarbonitrile, 22b. As a clear oil that decomposed upon standing (R_f 0.40, 60:40, hexanes:ethyl acetate). IR (oil) 3062, 2986, 2903, 1786, 1686, 1597, 1449, 1415, 1380, 1322, 1268 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (d, J = 6.3 Hz, 3H), 3.40 (d, J = 7.2 Hz, 2H), 3.51−3.54 (m, 1H), 4.00 (d, J = 8.7 Hz, 1H), 4.95−4.99 (m, 1H), 7.48−7.54 (m, 2H), 7.61−7.65 (m, 1H), 7.95−8.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.1, 36.2, 36.9, 39.8, 78.5, 114.4, 128.0, 128.8, 128.9, 134.0, 166.9, 196.2; MS (M^+, %) 243 ($M^{\bullet+}$, 21), 159 (18), 120 (18), 105 (100), 77 (52). HRMS Calcd for $C_{14}H_{13}NO_3$: 243.0895; found: 243.0905.

(±)-2-Oxo-4-(2-oxo-2-phenylethyl)-tetrahydro-3-furancarbonitrile, 23b. As a viscous oil that decomposed upon standing (R_f 0.36, 60:40, hexanes:ethyl acetate). IR (oil) 2924, 1799, 1682, 1596, 1451, 1376, 1162 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.21 (dd, J = 8.7, 18.0 Hz, 1H), 3.46 (ddddd, J = 4.8, 6.3, 7.2, 8.7, 9.0 Hz, 1H), 3.58−3.65 (dd, J = 4.8, 18.0 Hz, 1H), 3.66 (d, J = 6.3 Hz, 1H), 4.08 (dd, J = 9.0, 9.3 Hz, 1H), 4.87−4.92 (dd, J = 7.2, 9.3 Hz, 1H), 7.26−7.54 (m, 2H), 7.59−7.65 (m, 1H), 7.91−7.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.9, 37.6, 39.2, 72.0, 114.1, 128.1, 129.0, 134.2, 135.6, 167.3, 196.0; MS (M^+, %) 292.2 ($M^{\bullet+}$, 28), 145 (38), 120 (32), 105 (100), 77 (50). HRMS Calcd for $C_{13}H_{11}NO_3$: 229.0739; found: 229.0741.

General Lactonization Procedure Using Ethyl Acetoacetate. To a solution of sodium ethoxide (0.5 M, 4.4 mL, 2.2 mmol) and THF (4 mL) was added ethyl acetoacetate **8c** (2.1 mmol), and the reaction was stirred for 15 min under an N_2 atmosphere To this solution was added the 1,2-dioxine (1 mmol), and the reaction was stirred for 16 h. After this period, the reaction was quenched by the addition of 1 M HCl (2 mL) and the mixture partitioned between dichloromethane (50 mL) and 1 M HCl (50 mL). The aqueous layer was then extracted, the subsequent organic layers were dried and filtered, and the solvent was removed under reduced pressure. Column chromatography (60:40, hexanes:ethyl acetate) yielded the following substituted lactones:

(±)-3-Acetyl-4-(2-oxo-2-phenylethyl)-5-phenyltetrahydro-2-furanone, 9c. As colorless needles, mp 113−114 °C (R_f 0.25, dichloromethane). IR (Nujol) 1769, 1714, 1677, 1459, 1379, 1341, 1237, 1164 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.52 (s, 3H), 2.59 (dd, J = 4.2, 18.3 Hz, 1H), 2.85 (dd, J = 4.5, 18.3 Hz, 1H), 3.71 (d, J = 7.4 Hz, 1H), 3.84 (dddd, J = 4.2, 4.5, 7.4, 7.4 Hz, 1H), 5.95 (d, J = 7.4 Hz, 1H), 7.17−7.20 (m, 2H), 7.26−7.55 (m, 6H), 7.66−7.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.6, 38.0, 38.1, 58.6, 82.2, 125.6, 127.7, 128.2, 128.6, 128.6, 128.8, 133.5, 135.5, 136.1, 171.1, 197.6, 200.1; MS (M^+, %) 323 ($M^{\bullet+}$ + H, 5), 202 (100), 160 (30), 105 (75). Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63%. Found, C, 74.56; H, 5.79%.

(±)-3-Acetyl-5-methyl-4-(2-oxo-2-phenylethyl)-tetrahydro-2-furanone, 22c. As white crystals, mp 80−81 °C (R_f 0.23, 70:30, hexanes:ethyl acetate). IR (Nujol) 2983, 1767, 1717, 1683, 1597, 1449, 1357 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (d, J = 6.6 Hz, 3H), 2.47 (s, 3H), 3.10−3.30 (m, 2H), 3.51−3.57 (m, 2H), 5.06 (dq, J = 6.6, 6.6 Hz, 1H), 7.45−7.51 (m, 2H), 7.58−7.63 (m, 1H), 7.92−7.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.0, 29.5, 36.3, 37.2, 58.2, 77.6, 127.9, 128.7, 133.6, 136.0, 171.3, 197.4, 200.2; MS (M^+, %) 261 ($M^{\bullet+}$ + H, 25), 218 (10), 159 (14), 105 (100). Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.19%. Found, C, 69.29; H, 6.37%.

(±)-3-Acetyl-4-(2-oxo-2-phenylethyl)-tetrahydro-2-furanone, 23c. As white plates, mp 114−115 °C. (R_f 0.21, 70:30, hexanes:ethyl acetate). IR (Nujol) 1769, 1713, 1676, 1597, 1580, 1012 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.48 (s, 3H), 3.11−3.16 (m, 1H), 3.31−3.34 (m, 1H), 3.51−3.57 (m, 2H), 4.69−4.73 (m, 1H), 7.47−7.50 (m, 2H), 7.59−7.61 (m, 1H), 7.92−7.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.6, 33.2, 40.8, 58.5, 71.8, 127.9, 128.8, 133.7, 136.0, 171.8, 197.2, 200.0; MS ($M^{\bullet+}$, %) 247 ($M^{\bullet+}$ + H, 10), 145 (20), 120 (50), 105 (100). Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73%. Found, C, 68.35; H, 5.62%.

General Procedure for Alkylation of Lactone 9a. To a solution of sodium ethoxide (0.5 M, 2.2 mL) and THF (4 mL) was added diethyl malonate **8a** (1 mmol), and the reaction was stirred for 15 min under an N_2 atmosphere. To this solution was added **6a** (1 mmol), and the reaction was stirred for 16 h. After this period, alkyl halide (1.05 mmol) was added and the reaction stirred overnight (16 h) at room temperature. The reaction was quenched by the addition of 1 M HCl (2 mL) and the mixture partitioned between dichloromethane (50 mL)

and 1 M HCl (50 mL). The aqueous layer was then extracted, the subsequent organic layers were dried and filtered, and the solvent was removed under reduced pressure. Column chromatography (60:40, hexanes:ethyl acetate) yielded the following lactones;

(±)-Ethyl 3-Methyl-2-oxo-4-(2-oxo-2-phenylethyl)-5-phenyltetrahydro-3-furancarboxylate, 12. Obtained as a mixture of isomers epimeric at C_3 (as determined by ^{1}H NMR) which were not separated but decarboxylated. Hence, **12** was refluxed in 50% AcOH (5 mL) for 16 h, and the resultant mixture was cooled and basified. The aqueous layer was then extracted with dichloromethane (20 mL), the resultant organic layer dried and filtered, and the solvent removed under reduced pressure. This yielded two products (65:35 mixture by ^{1}H NMR) which were separated by chromatography (70:30, hexanes:ethyl acetate) and identified as the following:

(±)-3-Methyl-4-(2-oxo-2-phenylethyl)-5-phenyltetrahydro-3-furanone, 13a. As colorless plates, mp 147−149 °C (R_f 0.53, 60:40, hexanes:ethyl acetate). IR (Nujol) 1758, 1683, 1376, 1349, 1163 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) d 1.28 (d, J = 7.2 Hz, 3H), 2.61−2.66 (dq, J = 7.2, 7.2 Hz, 1H), 2.70−2.75 (dddd, J = 4.8, 7.2, 7.2, 9.0 Hz, 1H), 3.11−3.15 (dd, J = 7.2, 16.8 Hz, 1H), 3.20−3.23 (dd, J = 4.8, 16.8 Hz, 1H), 5.12 (d, J = 9.0 Hz, 1H), 7.32−7.43 (m, 7H), 7.54−7.57 (m, 1H), 7.79−7.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.5, 38.7, 41.9, 48.1, 83.8, 126.6, 128.0, 128.8, 129.1, 133.6, 136.5, 137.3, 170.2, 197.3 (one aromatic masked); MS (M^+, %) 295 ($M^{\bullet+}$, 100), 174 (25), 105 (20). Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H: 6.16%. Found: C, 77.88; H, 6.08%.

(±)-3-Methyl-4-(2-oxo-2-phenylethyl)-5-phenyltetrahydro-3-furanone 13b. As colorless prisms, mp 158−160 °C (R_f 0.68, 60:40, hexanes:ethyl acetate). IR (Nujol) 1755, 1679, 1376, 1350, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.18 (d, J = 7.8 Hz, 3H), 3.03 (dq, J = 7.2, 7.8 Hz, 1H), 3.09−3.20 (m, 3H), 5.22 (d, J = 4.8 Hz, 1H), 7.32−7.35 (m, 1H), 7.38−7.40 (m, 2H), 7.45−7.48 (m, 4H), 7.57−7.60 (m, 1H), 7.93−7.95 (m, 2H); MS (M^+, %) 295 ($M^{\bullet+}$, 30), 175 (15), 174 (62), 105 (100), 77 (25). HRMS Calcd for $C_{19}H_{18}O_3$ 294.1256. found, 294.1244.

(±)-Ethyl 3-Methyl-2-oxo-4-(2-oxo-2-phenylethyl)-5-phenyltetrahydro-3-furancarboxylate, 14. Obtained as a colorless oil (R_f 0.53, 60:40, hexanes:ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, J = 7.2 Hz, 3H), 2.62−2.71 (dd, J = 9.0, 18.9 Hz, 1H), 2.95−3.03 (dd, J = 5.1, 18.9 Hz, 1H), 3.35 (d, J = 13.8 Hz, 1H), 3.53 (d, J = 13.8 Hz, 1H), 3.80−3.88 (ddd, J = 5.1, 9.0, 9.3 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 5.21 (d, J = 9.3 Hz, 1H), 7.08−7.21 (m, 5H), 7.30−7.40 (m, 7H), 7.50−7.55 (m, 1H), 7.62−7.66 (m, 2H); MS (M^+, %) 443.4 ($M^{\bullet+}$, 100), 221.1 (38), 105.1 (25). **14** was decarboxylated under basic conditions. Hence, **14** was stirred in a mixture of ethanol (10 mL) and KOH (2 M, 10 mL) for 16 h. After this period, the mixture was acidified, the aqueous layer extracted with dichloromethane (20 mL), the resultant organic layer dried and filtered, and the solvent removed under reduced pressure. The residue was then dissolved in toluene (10 mL) and refluxed overnight. The toluene was then removed under reduced pressure and the residue purified by chromatography to yield the following:

(±)-3-Benzyl-4-(2-oxo-2-phenylethyl)-5-phenyltetrahydro-3-furanone, 15. White solid, mp 96−97.5 °C (R_f 0.65, 60:40, hexanes:ethyl acetate). IR (Nujol) 1776, 1679, 1340, 1164 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.75 (dddd, J = 5.4, 6.3, 8.1, 9.3 Hz, 1H), 2.88 (dd, J = 5.4, 17.1 Hz, 1H), 2.94 (dd, J = 7.8, 13.8 Hz, 1H), 2.97 (dd, J = 6.3, 17.1 Hz, 1H), 3.14 (ddd, J = 4.8, 7.8, 9.3 Hz, 1H), 3.24 (dd, J = 4.8, 13.8 Hz, 1H), 5.25 (d, J = 8.1 Hz, 1H), 7.10−7.20 (m, 8H), 7.28−7.30 (m, 2H), 7.35−7.40 (m, 2H), 7.51−7.57 (m, 1H), 7.63−7.66 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 35.5, 38.6, 44.6, 47.0, 83.6, 126.3, 126.7, 127.8, 128.5, 128.6, 128.7, 129.2, 131.0, 133.3, 136.3, 137.7, 137.9, 177.3, 197.6; MS (M^+, %) 371 ($M^{\bullet+}$, 28), 250 (29), 159 (82), 105 (100), 77 (35). Anal. Calcd for $C_{25}H_{22}O_3$: C, 81.06; H: 5.99%. Found: C, 80.78; H, 5.98%.

General Procedure for the Synthesis of Optically Enriched Lactones 31−33. To a solution of the chiral cobalt(II) complex (**29**, **30a**, or **30b**) (0.075 mmol) in dry THF (5.0 mL) at −4 °C under N_2 was added **6a** (0.238 g, 1.0 mmol), and the mixture was stirred until complete conversion of the 1,2-dioxine to the enone (as determined by TLC; approximately 3 h). After this period, a solution of the ester (**8a** and **8b**, 1.0 mmol; **8c**, 2.0 mmol) in sodium ethoxide (0.5 M, **8a** and **8b**, 1.05 mmol; **8c**, 2.1 mmol) was added and the reaction stirred for a further 16 h at room temperature. After this period 1 M HCL (2.0 mL) was added and the aqueous layer extracted with dichloromethane (20.0 mL). The resultant organic layers were dried and filtered, the solvent was removed under reduced pressure, and the lactone was purified by chromatography (60:40 hexanes:ethyl acetate). Spectral data for each lactone (**31**, **32**, and **33**) was identical as for their racemic counterparts (**9a**−**c**). The enantiomeric excess (ee) for each lactone was determined as follows: lactone (approximately 6 mg) was dissolved in a 1:4, d_6-benzene:CCl_4 solution and chiral shift reagent europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] complex added until baseline separation was attained. The following ^{1}H signals were chosen: **31** (C*H*Ph); **33** (C(O)C*H*$_3$); ee could not be established for lactone **32** due to insolubility in the d_6-benzene−CCl_4 solvent system.

(+)-(3*S*,4*S*,5*S*)-3-(4-Bromobenzyl)-4-(2-oxo-2-phenylethyl)-5-phenyltetrahydro-2-furanone, **35.** To a solution of enantioenriched **31b** (0.209 g, 0.593 mmol) in dry THF (5.0 mL) under N_2 was added sodium ethoxide (1.31 mL, 0.5 M), and the solution was stirred for 30 min. 4-Bromobenzyl bromide (0.163 g, 0.652 mmol) was then added and the reaction stirred for a further 16 h at room temperature. The reaction was then treated with KOH (2 M, 2.0 mL) and stirred overnight at room temperature. The mixture was then acidified by the addition of 1 M HCl and the reaction diluted with CH_2Cl_2 (10.0 mL) and partitioned with brine solution (10.0 mL). The aqueous layer was extracted with CH_2Cl_2 (10.0 mL), the resultant organic layers were combined, dried, and filtered, and the solvent was removed under reduced pressure. The crude acid was then dissolved in toluene (10.0 mL) and refluxed for 16 h. The toluene was then removed under reduced pressure and the crude product purified by column chromatography to yield the title compound as a white solid (0.160 g, 0.356 mmol). The product was recrystallized three times from CH_2Cl_2/hexanes to yield enantiopure **35**. Enantiopurity was determined by chiral shift reagent as previously stated above; the following ^{1}H signal was chosen (C*H*Ph). Obtained as a white solid, mp 129−131 °C (R_f 0.63, 60:40, hexanes:ethyl acetate); $[\alpha]^{20}_D$ 48.38° (c 0.62 M, $CHCl_3$). IR (Nujol) 1783, 1681, 1162 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.71−2.79 (m, 1H), 2.90−3.10 (m, 4H), 3.18 (dd, J = 4.8, 13.5 Hz, 1H), 5.23 (d, J = 8.7 Hz, 1H), 7.03−7.14 (m, 4H), 7.28−7.35 (m, 3H), 7.39−7.45 (m, 2H), 7.55−7.60 (m, 1H), 7.68−7.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.8, 38.8, 44.4, 47.2, 83.7, 120.8, 126.2, 127.8, 128.7, 128.8, 128.9, 131.2, 131.7, 133.6, 136.2, 137.7, 137.8, 177.1, 197.5. MS (M^+, %) 450 ($M^{\bullet+}$, 15), 448 (10), 250 (60), 159 (60), 105 (100). HRMS Calcd for $C_{25}H_{21}BrO_3$ 448.0675. found, 448.0660. X-ray quality crystals were obtained by recrystallization from CH_2Cl_2/hexanes.

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Supporting Information Available: X-ray crystallographic data for **9c** and **35** and ORTEP diagrams of structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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