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Template-directed C–H activation: development and application to the total synthesis of 7-episordidin

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Abstract—The development of a template-directed C–H activation strategy and its application to the diastereoselective synthesis of (±)-7-episordidin, an aggregation pheromone from the male banana weevil, *Cosmopolites sordidus* Germar, is reported. The key step of the synthetic route is a regioselective rhodium(II)-catalyzed diazocarbonyl C–H activation reaction that simultaneously generates three of the four stereocenters present in the natural product.

1. Introduction

Over the last two decades, the dirhodium(II)-catalyzed decomposition of α-diazocarbonyl compounds and intramolecular C–H insertion of the resulting Rh carbenoids has emerged as a particularly powerful methodology for the construction of carbocyclic and heterocyclic rings.[1,2] Extensive efforts by a number of groups to systematically identify the factors which control the site-selectivity of intramolecular C–H insertion reactions have revealed that, in the absence of overriding conformational influences, the formation of five-membered rings is highly favored. Furthermore, in competitive situations the relative reactivity of carbon–hydrogen bonds is in the order tertiary>secondary≫primary and significantly, there is a strong preference for insertion into C–H bonds alpha to heteroatoms such as nitrogen[3] and oxygen.[4] This C–H activation has been presented as evidence[4,5] that insertion proceeds with C–H bond polarization and concomitant charge development on carbon which is stabilized by heteroatoms through resonance effects.[6] As shown in Fig. 1, insertion into oxygen-activated C–H bonds can be considered to be the synthetic equivalent of an aldol-type reaction and as such is potentially very useful.[7] While the intramolecular variant of this transformation has been successfully exploited in the preparation of 3(2*H*)-furanones,[8] β-lactones,[9] tetrahydrofurans[10] and γ-butyrolactones,[11] there are potential pitfalls associated with its application in situations where multiple oxygen atoms are present in the insertion precursor. Of primary concern is the likelihood of competitive oxonium ylide formation.[12]

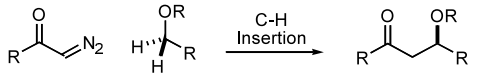

Figure 1. Insertion into oxygen-activated C–H bonds as an aldol surrogate.

It occurred to us that by temporarily restraining an α-diazo ketone and the oxygen-activated C–H bonds of a 1,3-diol **1** within a conformationally restricted template structure, we might be able to achieve C–H insertion and suppress side reactions, such as ylide formation. As outlined in Scheme 1, our strategy to realize this goal is centered around 2-carboxy-1,3-dioxanes which display a pronounced preference (∼4 kcal/mol) for the axially oriented 2-carboxylate group.[13] The α-diazo ketones **2** derived from this ring system are suitable vehicles with which to explore our insertion strategy since the C-2 diazoacetyl group is positioned in a coplanar arrangement with the activated C–H bonds at C-4/6. Thus configured, **2** are poised for transannular C–H insertion to form 2,8-dioxabicyclo[3.2.1]octanones **3** which can be viewed as masked aldol products to be revealed by cleavage of the furanone ring (**3**→**5**).[14] Alternatively, **3** is the core structure present in both the

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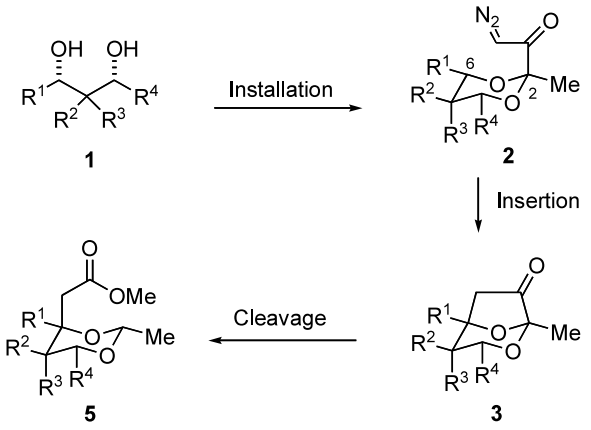


Scheme 1. Template-directed C–H activation.

zaragozic acid[15] and the sordidin family of insect pheromones.[16] For symmetrical substrates **2** ($R_1 = R_4$) the possibility of desymmetrization through the use of chiral catalysts was additionally appealing, since up to four stereocenters could potentially be generated in a single transformation. Herein, we report the development of this C–H activation strategy and its application to the first diastereoselective total synthesis of the natural product 7-episordidin.

2. Results and discussion

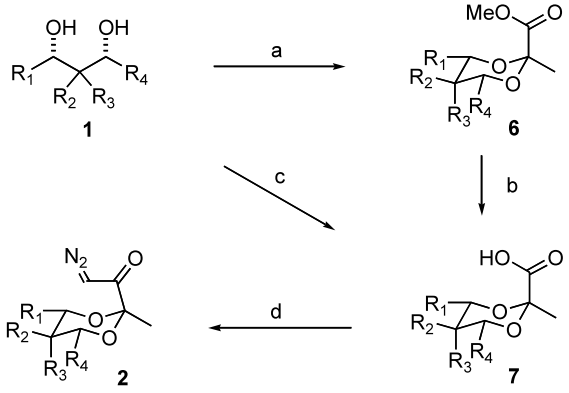
2.1. Preparation of 2,8-dioxabicyclo[3.2.1]octanones

Our investigation began with the preparation of a range of pyruvic acid acetals **6** following a protocol reported by Ziegler.[17] Thus, treatment of a solution of **1a–d**, (Table 1, entries 1–4) in acetonitrile with $BF_3{\cdot}Et_2O$ (2 equiv.) and methyl pyruvate (2 equiv.) gave **6**, which were then saponified to furnish the corresponding carboxylic acids **7**. Reaction of 2-methyl-2-nitromethylpropane-1,3-diol (**1g**) with methyl pyruvate generated an 8.6:1 mixture of the C-5 diastereomers **6g** and **6h** which were separated by column chromatography on silica gel (Table 1, entries 7–8).[18] The relative configuration of nitro-substituted acetal **6g** was determined by X-ray crystallographic analysis.[19] Saponification of esters **6g** and **6h**, as before, then gave the corresponding carboxylic acids. Substrates **7e–f** (entries 5–6), on the other hand were prepared by acid-catalyzed acetalization of **1e–f** (1.5 equiv.) and pyruvic acid (1.0 equiv.) followed by saponification of the resulting mixture of ester products.[20] In the case of **1b** (entry 2) and **1f** (entry 6) acetalization provided a single diastereomer in which the C-2 carboxylate group was found to be in the axial orientation, *trans* to the equatorial ring substituents. The assignment of the acetal stereochemistry in these cases was achieved using ^{13}C NMR spectroscopy, examining the C-2 methyl groups which are known to be sensitive to the relative configuration of the adjoining acetal.[21] The ^{13}C NMR spectra of **7b** and **7f** showed methyl signals at 26.8 and 26.6 ppm respectively, thereby confirming their equatorial position.

Although it was now expected that we could access **2** from **7**, via the corresponding acid chlorides, all attempts to prepare the latter compounds using thionyl chloride ($SOCl_2$) or other chlorinating agents proved unsuccessful. In all substrates examined, addition of $SOCl_2$ to **7** resulted in rapid decomposition.[22] Reasoning that a less activated carboxylate derivative would be more stable yet retain sufficient reactivity to undergo the Arndt–Eistert synthesis, the mixed anhydrides were prepared by treating a solution of **7** with Et_3N and isobutyl chloroformate.[23] Addition of an ethereal solution of diazomethane to the reaction mixture then provided the α-diazo ketones **2** in good yield.

With a protocol for the diastereoselective preparation of **2** established, attention now turned to the C–H insertion. Thus, slow addition of **2a** to dirhodium(II) tetraacetate ($Rh_2(O_2CCH_3)_4$) (2 mol%) in CH_2Cl_2 afforded 2,8-dioxabicyclo[3.2.1]octanone **3a**, the product of transannular C–H insertion, in 52% yield together with a small amount of **4a** (4%) (Table 2, entry 1). This bicyclic enol ether proved to be rather unstable to silica gel chromatography in addition to being volatile. Cyclization of substrates **2b–e** (entries 4–7) under these conditions provided similar yields of **3**, while **4** was isolated from the reactions of **2c** and **2d** only. Diazo decomposition of **2f** (entry 8) gave an inseparable mixture (19:13, ^1H NMR) of C-4 and C-6

Table 1. Preparation of 2-diazoacetyl-1,3-dioxanes **2**



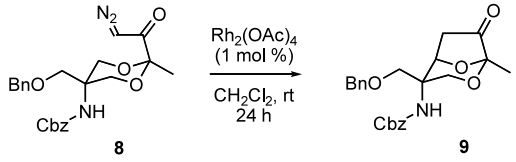
Entry	1	R_1	R_2	R_3	R_4	Method[a]	2	Yield (%)[b]
1	**1a**	H	Me	Me	H	a, b, d	**2a**	61
2	**1b**	Me	H	H	Me	a, b, d	**2b**	80
3	**1c**	H	Et	Et	H	a, b, d	**2c**	60
4	**1d**	H	-$(CH_2)_4$-		H	a, b, d	**2d**	68
5	**1e**	H	H	H	H	c, d	**2e**	49
6	**1f**	Me	H	H	H	c, d	**2f**	64
7	**1g**	H	Me	NO_2	H	a, b, d	**2g**	45
8	**1g**	H	NO_2	Me	H	a, b, d	**2h**	6

[a] *Methods*: (a) $MeCOCO_2Me$, $BF_3{\cdot}Et_2O$, CH_3CN, rt, 16 h; (b) NaOH, THF, H_2O, reflux, 5 h; (c) i. $MeCOCO_2H$, Amberlite IR-120, PhH, reflux 16 h; (ii) NaOH, H_2O, reflux, 2 h; (d) i. Et_3N, CH_2Cl_2, −20°C; (ii) *i*-BuOCOCl, −20°C, 5 min; (iii) CH_2N_2, Et_2O, −20°C to rt, 16 h.

[b] Overall yield of **2** from **1**, after purification by silica gel column chromatography.

insertion products. While the known preference for insertion to occur at tertiary C–H bonds should favor insertion at C-6,[2] the alternative insertion process at C-4, which generates a tertiary rather than a quaternary center, may encounter less steric hindrance. Of note is the differing reactivity displayed by diastereomers **2g** and **2h**. In the case of **2h**, $Rh_2(O_2CCH_3)_4$ promoted decomposition gave **3h** (entry 10), albeit in low yield, while no trace of **3g** could be detected in the crude reaction mixture of the C-5 epimer, **2g** (entry 9). The inhibitory effect of electron withdrawing groups upon carbenoid C–H insertion has previously been reported.[24] The axial C-4/6 C–H bonds of **2g** are antiperiplanar to the C-5 nitro group and should therefore be more deactivated towards insertion than those in **2h** which are gauche to the electron withdrawing group.[25]

In contrast to substrate **2g**,[26] compound **8** underwent insertion to provide the expected bicycle **9** in 42% yield (Scheme 2). In this case, the less electron-withdrawing axial C-5 carbamate group does not appear to inhibit insertion at the adjoining C–H bonds.

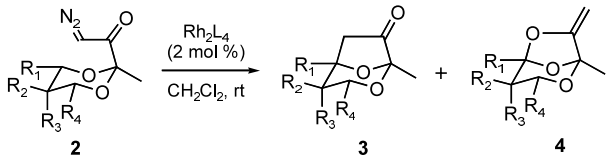


Scheme 2.

With regard to the formation of **4**, Clark and co-workers have recently reported the formation of analogous products during a study of the rhodium(II)-mediated decomposition of α-diazo-α′-alkoxy ketones.[27] According to Clark's mechanistic rationale, the rhodium carbenoid species **10**, generated upon diazo decomposition of **2a**, faces two possible fates: (i) concerted C–H insertion to form 3(2*H*)-furanone **4a** or, (ii) oxygen-assisted hydride transfer[28] to the electron-deficient carbene center generating oxonium ion-rhodium enolate species **11**.[29] Cyclization of **11**, or its enol tautomer **12**, could then generate **4a** (Scheme 3). Hydride transfers have recently been reported by Doyle, White and others[27] who note that this process becomes prevalent when the oxonium ion species **11**/**12** are stabilized.[30] Our substrates seem to fit this pattern since the axial lone pairs of the ring oxygens are positioned antiperiplanar to the departing hydrogen atom.

Reasoning that a less electrophilic catalyst might suppress hydride transfer and favor insertion, dirhodium(II) tetra(caprolactamate) ($Rh_2(cap)_4$) was examined as a catalyst.[29b] However, decomposition of **2a** was prohibitively slow at room temperature and only proceeded upon heating for 72 h. The yields of **3a** and **4a** in this case were similar to those found with $Rh_2(O_2CCH_3)_4$ (Table 2, entry 2). It appears that bis-α-alkoxy-α′-diazoketones **2** are more resistant to diazo

Table 2. Preparation of 2,8-diazobicyclo[3.2.1]octanones **3**



Entry	**2**	Method[a]	Yield (%), **3**[b]	Yield (%), **4**[b]
1	**2a**	a	52	4
2	**2a**	b	45	5
3	**2a**[c]	c	–	–
4	**2b**	a	43	–
5	**2c**	a	42	12
6	**2d**	a	50	11
7	**2e**	a	44	–
8	**2f**	a	54[d]	–
9	**2g**[e]	a	–	–
10	**2h**	a	27	–

[a] *Methods*: (a) A solution of **2** in CH_2Cl_2 was added via syringe pump to a solution of $Rh_2(O_2CCH_3)_4$ (2 mol%) in CH_2Cl_2 (0.023 M), over 20 h; (b) A solution of **2** in CH_2Cl_2 was added via syringe pump to a solution of $Rh_2(cap)_4$ (2 mol%) in CH_2Cl_2, at reflux, over 72 h; (c) A solution of **2a** in CH_2Cl_2 was added via syringe pump to a solution of $Rh_2(O_2CCF_3)_4$ (2 mol%) in CH_2Cl_2, over 20 h.

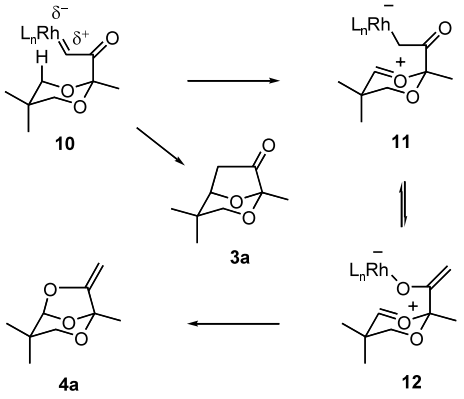
[b] Yields of **3** and **4** after purification by silica gel chromatography.

[c] Treatment of **2a** with $Rh_2(O_2CCF_3)_4$ generated a complex mixture of products.

[d] **3f** was isolated as an inseparable (19:13, ^1H NMR) mixture of C-4 and C-6 C–H insertion products.

[e] Diazo decomposition of **2g** generated a complex mixture of products which did not contain **3g**.

decomposition than other α-diazo ketones which may be due to the electron-withdrawing effect of the acetal group adjoining the diazo center. On the other hand, treatment of **2a** with dirhodium(II) tetra(trifluoroacetate) ($Rh_2(O_2CCF_3)_4$) resulted in a very complex reaction mixture which, as indicated by ^1H NMR spectroscopy, did not contain the insertion product **3a** (entry 3). It appears that, in this case, hydride transfer is the dominant pathway but the enol ether generated is unstable in the presence of the electrophile catalyst and decomposes during the reaction. Indeed, exposure of **4a** to $Rh_2(O_2CCF_3)_4$ in CH_2Cl_2 led to extensive decomposition.



Scheme 3.

2.2. Total synthesis of (±)-7-episordidin

Having established a protocol to access 2,8-bicyclo[3.2.1]octanones, we now proceeded to evaluate this methodology through its application to natural product synthesis and specifically to the development of a route to the insect aggregation pheromone (±)-7-episordidin.[16] The banana weevil, *Cosmopolites sordidus* Germar, is a widespread and highly destructive pest of banana trees.[31] The impact on crop production is particularly acute since current methods for controlling this insect are hampered by its longevity, propensity to reproduce, and resistance to most classes of insecticides. In 1993, Budenberg first reported evidence that the male of this species releases a volatile aggregation pheromone.[32] The major component of this mixture, 1-ethyl-3,5,7-trimethyl-2,8-dioxabicyclo[3.2.1]octane (**13a**), was subsequently isolated, identified, and synthesized by Ducrot and co-workers who assigned it the trivial name sordidin (Fig. 2).[33a] More recently, Kitching has shown that, in addition to **13a**, 7-episordidin (**13b**) is also released by *C. sordidus* from Australia,[33d] while Oehlschlager reported that all four isomers of sordidin (**13a**–**d**) are produced by weevils collected in Kenya.[33b] Field trials in Costa Rica[31] have shown that traps baited with mixtures of **13** have a high capture rate and offer a viable method for controlling the population this pest. Since the natural abundance of these pheromones is very low (1500 weevils yield ca. 100 μg), synthesis provides the only practical method for securing quantities of **13**. All reported syntheses of the sordidin family involve formation of the acetal moiety through acid-catalyzed cyclization of the corresponding acyclic keto-1,3-diols.[33] Under these conditions, however, the C-7 stereocenter readily epimerizes and mixtures of diastereomers are obtained. To date, no stereoselective syntheses of **13** have been reported.

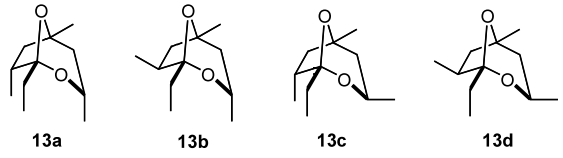
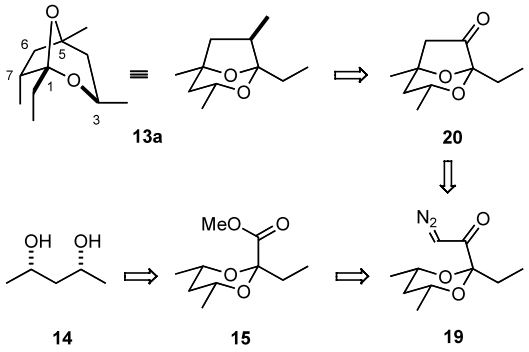


Figure 2.

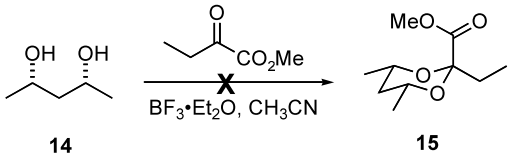
As outlined in Scheme 4, we envisioned **13a** arising from ketone **20**, which could, in turn, be accessed through the metal-catalyzed intramolecular C–H insertion of symmetric diazoketone **19**. In this way, three of the four stereocenters present in the target molecule would be established in a single transformation. With regards to the regioselectivity of this process, we expected that insertion into the C-1 ethyl side chain would be highly disfavored over the axial C-4/6 C–H bonds of **19** since these bonds are activated by the adjoining oxygens atoms.[2]

Given the ease with which we had prepared simple pyruvate acetals in our initial study (Table 1), our opening efforts to prepare acetal **15** focused on direct acetalization of methyl 2-oxopropylbutyrate and *cis*-2,4-pentanediol **14** (Scheme 5).[34] Unfortunately, all attempts

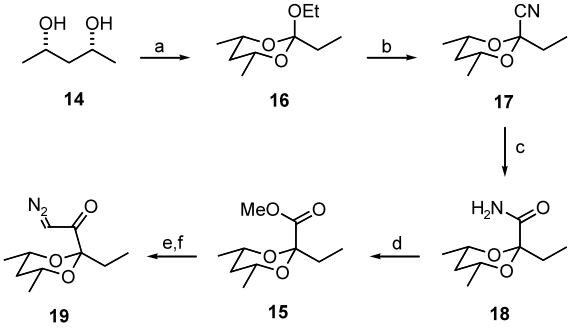


Scheme 4.

to achieve this goal using a variety of conditions led only to the decomposition of diol **14**. Accordingly, we opted to follow a stepwise approach to **15**, which we had previously developed during our synthesis of the dioxabicyclooctane core of the zaragozic acid family (Scheme 6).[16] Thus, **14** was treated with triethyl orthopropionate in the presence of a catalytic amount of *p*-TsOH to generate ortho ester **16** which was immediately treated in situ with trimethylsilyl cyanide and $BF_3{\cdot}Et_2O$. Upon stirring at room temperature for 16 h, cyanation proceeded with retention of configuration to furnish 2-cyano-1,3-dioxane **17** as a single diastereomer.[35] Hydrolysis of this nitrile with alkaline hydrogen peroxide then gave **18** in excellent overall yield from **14**. The relative configuration of **18** was confirmed by a NOESY experiment, which revealed correlations between the axial protons at C-4/6 and the amide protons.



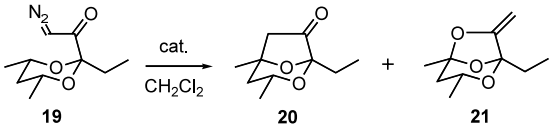
Scheme 5.



Scheme 6. *Reagents and conditions*: (a) $CH_3CH_2C(OEt)_3$, *p*-TsOH (2 mol%), CH_2Cl_2, rt, 16 h; (b) Me_3SiCN, $BF_3{\cdot}Et_2O$ (10 mol%), CH_2Cl, rt, 16 h, 99%; (c) NaOH, H_2O_2, EtOH, reflux, 3 h, 91%; (d) DMF–DMA (3 equiv.), MeOH, 110°C (sealed tube), 48 h, 97%; (e) NaOH, H_2O, THF, reflux, 16 h, 98%; (f) i. Et_3N, *i*-BuOCOCl, CH_2Cl_2, −20°C, 5 min, ii. CH_2N_2, Et_2O, −20°C to rt, 16 h, 96%.

Although the prospect of now converting **18** to the corresponding methyl ester **15** was somewhat daunting, Brocchetta and co-workers recently reported the use of dimethylformamide dimethyl acetal (DMF–DMA) as a mild reagent for this traditionally difficult transformation.[36] Gratifyingly, upon heating **18** and DMF–DMA in anhydrous methanol at 110°C in a sealed tube for 48 h, ester **15** was formed in 97% yield. Diazoketone **19** was prepared in 94% overall yield by a sequence of saponification, mixed-anhydride formation and in situ treatment with diazomethane. With quantities of **19** available, we now proceeded to evaluate a range of catalysts for C–H activation; the results of this study are summarized in Table 3. In all cases diazo decomposition of **19** led to the formation of **20**, the product of transannular C–H insertion, as well as bicyclic enol ether **21**. As anticipated, products arising from insertion into the C–H bonds of the ethyl chain were not observed under any conditions. It is clear from Table 3 that $Rh_2(OAc)_4$ (entry 1) was the most efficient catalyst for effecting cyclization while chiral dirhodium(II) tetracarboxylates (entries 2–4) and tetracarboxyamides (entry 5) failed to provide improvement in efficiency or useful levels of asymmetric induction. Copper salts (entries 6–8) were also investigated but gave only modest yields of C–H insertion. The more electrophilic copper carbenoids appear to favor the formation of **21** through the hydride abstraction pathway.[37]

Table 3. Intramolecular C–H insertion of diazoketone **19**[a]



Entry	Catalyst[b]	Isolated yield (%)[c,d]		E.e. (%)[e,f]	
		20	**21**	**20**	**21**
1	$Rh_2(OAc)_4$[g]	58	28	–	–
2	$Rh_2(PTPA)_4$[38a,b]	36	10	20	10
3	$Rh_2(DOSP)_4$[38c]	31	0	7	–
4	$Rh_2(TBSP)_4$[38d]	17	5	<5	<5
5	$Rh_2(MEPY)_4$[38d]	11	8	<5	7
6	$Cu(acac)_2$[h]	15	30	–	–
7	$Cu(tfacac)_2$[h]	19	20	–	–
8	$Cu(hfacac)_2$[h]	7	17	–	–

[a] Unless otherwise noted, reactions were carried as follows: a solution of **19** (50 mg, 0.24 mmol) in CH_2Cl_2 was added via syringe pump to a solution of catalyst (2 mol%) in CH_2Cl_2 (0.015 M) at reflux, over 20 h.

[b] $Rh_2(PTPA)_4$ was prepared according to the method of Taber (see Ref. 38b). The other catalysts are available commercially.

[c] Yields after purification by flash chromatography.

[d] The mass balance consisted of polar, intractable material.

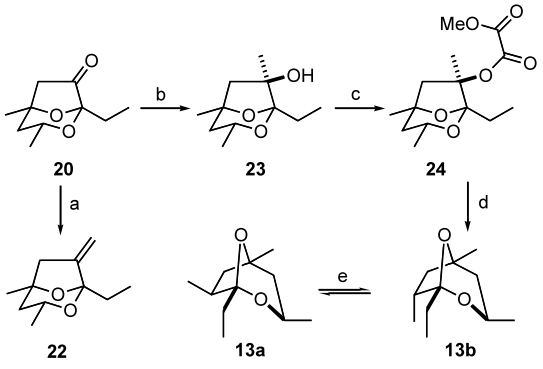
[e] Enantiomeric excesses were determined by capillary GC analysis prior to purification using a J&W cyclodex-B column.

[f] Absolute configuration was not determined.

[g] Reaction carried out on 8.5 mmol scale.

[h] 4 mol% catalyst used.

In view of the low levels of asymmetric induction observed during the cyclization of **19**, we now opted to complete our synthesis of **13b** with racemic **20**. Accordingly, we now attempted to install the remaining stereocenter at C-7 through a sequence of olefination and reduction. However, **22**, the α,β-unsaturated acetal generated upon Wittig methylenation of **20**, proved to be highly unstable and we were unable to isolate this material (Scheme 7).[39] Fortunately, addition of methylmagnesium iodide to **20** proceeded very efficiently to provide **23** as a single diastereomer. After considerable investigation, we found that this tertiary alcohol could be most effectively deoxygenated to generate **13b** using the method of Dolan and MacMillan.[40] Thus, sequential treatment of **23** with *n*-BuLi and methyl chlorooxoacetate gave **24** which, after purification, was heated with Bu_3SnH and AIBN in benzene for 16 h. The reaction mixture was then concentrated by distillation (1 atm) and the residue purified by radial chromatography (pentane/Et_2O, SiO_2) to provide (±)-7-episordidin (**13b**) as the sole reduction product. The moderate yield of this final transformation is primarily a reflection of the volatility of **13b**, which leads to significant losses during isolation. A comparison of the spectral and physical properties of our synthetic material (MS, IR and ^1H and ^{13}C NMR) with those reported by Mori[33e] indicated a close match.



Scheme 7. *Reagents and conditions*: (a) $Ph_3P{=}CH_2$, THF, rt, 16 h; (b) MeMgI, Et_2O, 0°C, 3 h, 98%; (c) *n*-BuLi, THF, −78°C, 5 min; (ii) $ClCOCO_2Me$, −78 to 0°C, 2 h, 78%; (d) Bu_3SnH (1.5 equiv.), AIBN (1.5 equiv.), PhH, reflux, 16 h, 50%; (e) *p*-TsOH, CH_2Cl_2 (Ref. 33e).

3. Summary

In summary, we have developed a novel method for the preparation of 2,8-dioxabicyclo[3.2.1]octanones **3** utilizing the Rh(II)-mediated C–H insertion of 2-diazoacetyl-1,3-dioxanes **2**. Furthermore, we also report the application of this template-directed insertion strategy to the first stereoselective synthesis of 7-episordidin (**13b**), which is accomplished in nine steps starting from *cis*-2,4-pentanediol (**2**), with an overall yield of 18%. Since the conversion of (±)-7-episordidin (**13b**) to sordidin (**13a**) has previously been described by Mori,[33e] the work reported herein also represents a formal synthesis of sordidin (**13a**).

4. Experimental

All reactions were carried out in oven- or flame-dried glassware under a nitrogen atmosphere, unless otherwise noted. All solvents were reagent grade. $BF_3{\cdot}Et_2O$ was distilled from calcium hydride, under reduced pressure, and stored under a nitrogen atmosphere. Triethylamine (Et_3N), acetonitrile (MeCN) and dichloromethane (CH_2Cl_2) were distilled from calcium hydride under dry nitrogen. Except as otherwise indicated, all reactions were magnetically stirred and monitored by thin-layer chromatography with Merck Kieselgel 60-F_{254}. Enantiomeric excesses of **20**/**21** were determined by capillary GC analysis prior to purification using a J&W cyclodex-B column. Flash column chromatography was carried out according to the method of Still on Merck silica gel 60 (mesh 230–400). All melting points were determined in an open capillary on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson genesis series FTIR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on either a Bruker Avance 400 (400 MHz ^1H, 100 MHz ^{13}C), Bruker Avance 500 (500 MHz ^1H, 125 MHz, ^{13}C), Bruker AM-400 (400 MHz, ^1H, 100 MHz, ^{13}C) or a Bruker AM-200 (200 MHz, ^1H, 50 MHz, ^{13}C) spectrometer. Chemical shift values (δ) are reported relative to chloroform (^1H δ 7.27 ppm, ^{13}C δ 77.23 ppm) or dimethylsulfoxide (^1H δ 2.50 ppm, ^{13}C δ 39.51 ppm). High-resolution electron impact (EI) mass spectra were obtained on a Kratos Concept 1H spectrometer at the University of Illinois Research Resources Center with a typical ionization voltage of 70 eV. High-resolution chemical ionization (CI) mass spectra were obtained on a FINNIGAN MAT 95 at the Mass Spectrometry Service Laboratory, University of Minnesota.

4.1. Representative procedure for the preparation of pyruvate ester acetals 6

4.1.1. 2-Carboxymethyl-2,5,5-trimethyl-1,3-dioxane, 6a. $BF_3{\cdot}Et_2O$ (21.70 g, 153.8 mmol) was added dropwise to a stirred solution of 2,2-dimethyl-1,3-propanediol (8.00 g, 76.9 mmol) and methyl pyruvate (15.70 g, 153.8 mmol) in MeCN (200 mL). The mixture was stirred for 16 h then quenched with saturated aqueous $NaHCO_3$ (60 mL) and allowed to stir for an additional 20 min. The resulting mixture was concentrated under reduced pressure to one third of its original volume. The concentrate was then extracted with CH_2Cl_2 (4×30 mL) and the combined organic extracts dried (Na_2SO_4) and concentrated. The resulting residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:1) to give **6a** (10.40 g, 72%): yellow oil; R_f 0.66 (EtOAc/hexanes, 1:1); IR (film) 2955, 2871, 1744, 1471, 1369, 1121, 1079, 1015, 882, 807, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.46 (s, 4H), 1.49 (s, 3H), 1.16 (s, 3H), 0.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 98.1, 73.4 (2 C), 52.5, 29.4, 25.8, 22.6, 21.8; high-resolution mass spectrum (CI) m/z 189.1132 [(M+H)$^+$; calcd for $C_9H_{17}O_4$ 189.1127].

4.1.2. *trans*-2-Carboxymethyl-*cis*-2,4,6-trimethyl-1,3-dioxane, 6b. (800 mg, 88%): yellow oil; R_f 0.18 (EtOAc/hexanes, 1:9); IR (film) 2974, 2938, 1745, 1440, 1385, 1266, 1112, 1052, 978, 817, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.81–3.73 (m, 2H), 3.72 (s, 3H), 1.45 (s, 3H), 1.41–1.40 (m, 1H) 1.23–1.20 (m, 1H), 1.15 (d, $J=6.2$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 98.8, 68.9 (2 C), 52.4, 39.4, 26.7 (2 C), 21.8; high-resolution mass spectrum (CI) m/z 189.1127 [(M+H)$^+$; calcd for $C_9H_{17}O_4$ 189.1127].

4.1.3. 2-Carboxymethyl-5,5-diethyl-2-methyl-1,3-dioxane, 6c. (1.06 g, 70%): yellow oil; R_f 0.24 (EtOAc/hexanes, 1:3); IR (film) 2966, 2877, 1745, 1460, 1376, 1265, 1118, 1031, 892, 805, 658 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.68 (d, $J=11.7$ Hz, 2H), 3.45 (d, $J=11.7$ Hz, 2H), 1.70 (q, $J=7.5$ Hz, 2H), 1.51 (s, 3H), 1.04 (q, $J=7.5$ Hz, 2H), 0.86 (t, $J=7.5$, 3H), 0.75 (t, $J=7.5$, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 98.4, 70.7 (2 C), 52.5, 34.1, 25.8, 24.3, 22.3, 7.6, 6.5; high-resolution mass spectrum (CI) m/z 217.1445 [(M+H)$^+$; calcd for $C_{11}H_{21}O_4$ 217.1440].

4.1.4. 8-Carboxymethyl-8-methyl-7,9-dioxaspiro[4.5]-decane, 6d. (1.14 g, 80%): yellow oil; R_f 0.38 (EtOAc/hexanes, 1:1); IR (film) 2962, 2807, 2103, 1724, 1647, 1334, 1280, 1192, 1132, 886, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.59–3.49 (m, 4H), 1.84–1.77 (m, 2H), 1.66–1.58 (m, 2H), 1.55–1.52 (m, 4H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 98.3, 72.4 (2 C), 52.6, 41.2, 34.5, 32.0, 26.0, 25.4, 24.7; high-resolution mass spectrum (CI) m/z 232.1538 [(M+NH$_4$)$^+$; calcd for $C_{11}H_{22}NO_4$ 232.1549].

4.1.5. *trans*-2-Carboxymethyl-2,5-dimethyl-5-nitro-1,3-dioxane, 6g. (11.99 g, 74%): white solid: mp 80–81°C; R_f 0.53 (EtOAc/hexanes, 1:1); IR (KBr) 2999, 2949, 1742, 1547, 1449, 1129, 909, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.72 (d, $J=11.9$ Hz, 2H), 3.86 (m, 5H), 1.51 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 98.7, 82.6, 67.8 (2 C), 53.3, 25.7, 19.9; high-resolution mass spectrum (CI) m/z 220.0828 [(M+H)$^+$; calcd for $C_8H_{14}NO_6$ 220.0821].

4.1.6. *cis*-2-Carboxymethyl-2,5-dimethyl-5-nitro-1,3-dioxane, 6h. (1.40 g, 9%): white solid: mp 79–80°C; R_f 0.26 (EtOAc/hexanes, 1:1); IR (KBr) 1744, 1539, 1275, 1184, 1125, 1075, 909, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.18 (d, $J=11.7$ Hz, 2H), 4.09 (d, $J=11.7$ Hz, 2H), 3.87 (s, 3H), 1.86 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 98.9, 79.5, 68.0 (2C), 53.4, 24.9, 22.0; high-resolution mass spectrum (CI) m/z 237.1093 [(M+NH$_4$)$^+$; calcd for $C_8H_{16}N_2O_6$ 237.1087].

4.2. Representative procedure for the preparation of pyruvate acid acetals 6 (Method A)

4.2.1. 2-Carboxy-2,5,5-trimethyl-1,3-dioxane, 7a. A solution of ester 6a (10.40 g, 0.06 mol) and NaOH (11.60 g, 0.27 mol) in a mixture of THF (100 mL) and H_2O (100 mL) was stirred at rt for 5 h. After cooling to 0°C, the reaction mixture was then acidified to pH 1 with ice cold 6 M aqueous H_3PO_4 (20 mL) and quickly

extracted with EtOAc (5×20 mL). The combined organic extracts were then dried (Na_2SO_4), and concentrated to provide 7a (8.20 g, 85%): white solid; mp 115–116°C; IR (KBr) 3503, 3957, 2871, 1719, 1198, 1138, 1073, 1011, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.56 (s, 1H), 3.54 (m, 4H), 1.58 (s, 3H), 1.18 (s, 3H), 0.73 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 175.9, 98.0, 73.7 (2 C), 29.6, 25.8, 22.7, 22.0; high-resolution mass spectrum (EI) m/z 129.0916 [$(M-CO_2H)^+$; calcd for $C_7H_{13}O_2$ 129.0916].

4.2.2. *trans*-2-Carboxy-*cis*-2,4,6-trimethyl-1,3-dioxane, 7b. (550 mg, 96%): white solid; mp 117–118°C; IR (KBr) 3058, 2982, 1733, 1320, 1207, 1152, 1098, 976, 912, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.95–3.87 (m, 2H), 1.60 (s, 3H), 1.51 (d, $J=13.2$ Hz, 1H), 1.33–1.31 (m, 1H), 1.26 (d, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 98.7, 69.3 (2 C), 39.35, 26.8, 21.9; high-resolution mass spectrum (CI) m/z 175.0981 [$(M+H)^+$; calcd for $C_8H_{15}O_4$ 175.0970].

4.2.3. 2-Carboxy-5,5-diethyl-2-methyl-1,3-dioxane, 7c. (930 mg, 99%): white solid; mp 122–23°C; IR (KBr) 3476, 2961, 1674, 1470, 1353, 1279, 1141, 1014, 952, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.74 (d, $J=11.6$ Hz, 2H), 3.52 (d, $J=11.6$ Hz, 2H), 1.71 (q, $J=7.5$ Hz, 2H), 1.59 (s, 3H), 1.10 (q, $J=7.5$ Hz, 2H), 0.86 (t, $J=7.5$ Hz, 3H), 0.75 (q, $J=7.5$ Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 176.1, 98.2, 71.0 (2 C), 34.4, 25.7, 24.4, 22.4, 7.7, 6.7; high-resolution mass spectrum (CI) m/z 203.1285 [$(M+H)^+$; calcd for $C_{10}H_{19}O_4$ 203.1283].

4.2.4. 8-Carboxy-8-methyl-7,9-dioxaspiro[4.5]decane, 7d. (550 mg, 86%): white solid; mp 127–28°C; IR (KBr) 2996, 2880, 1747, 1461, 1265, 1189, 1124, 1034, 879, 807 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.31 (bs, 1H), 3.69 (d, $J=11.2$ Hz, 2H), 3.62 (d, $J=11.2$ Hz, 2H), 1.84 (m, 2H), 1.70–1.63 (m, 2H), 1.59 (s, 3H), 1.58–1.54 (m, 2H) 1.16 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 175.9, 99.0, 72.3 (2 C), 41.1, 34.3, 31.9, 25.7, 25.3, 24.6; high-resolution mass spectrum (CI) m/z 218.1402 [$(M+NH_4)^+$; calcd for $C_{10}H_{20}NO_4$ 218.1392].

4.2.5. *trans*-2-Carboxy-2,5-dimethyl-5-nitro-1,3-dioxane, 7g. (1.85 g, 99%): white solid; mp 148–149°C; IR (KBr) 3007, 1708, 1543, 1451, 1268, 1142, 1075, 1044, 894, 681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.76 (d, $J=11.8$ Hz, 2H), 3.92 (d, $J=11.8$ Hz, 2H), 1.58 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 170.3, 97.9, 83.4, 66.9 (2 C), 25.2, 18.7; high-resolution mass spectrum (CI) m/z 223.0937 [$(M+NH_4)^+$ calcd for $C_7H_{15}N_2O_6$ 223.0930].

4.2.6. *cis*-2-Carboxy-2,5-dimethyl-5-nitro-1,3-dioxane, 7h. (830 mg, 99%): white solid; mp 127–128°C; IR (KBr) 3073, 1707, 1533, 1260, 1136, 1074, 906, 740, 493 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.29 (d, $J=11.8$ Hz, 2H), 4.11 (d, $J=11.8$ Hz, 2H), 1.84 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 98.1, 79.3, 67.5 (2C), 23.8, 21.4; high-resolution mass spectrum (CI) m/z 223.0941 [$(M+NH_4)^+$; calcd for $C_7H_{15}N_2O_6$ 223.0930].

4.3. Representative procedure for the preparation of pyruvate acid acetals 6 (Method B)

4.3.1. *trans*-2-Carboxy-*cis*-2,4-dimethyl-1,3-dioxane, 7f. A mixture of 1,3-butanediol (10.00 g, 111.1 mmol), pyruvic acid (6.50 g, 74.1 mmol) and Amberlite IR-120 (plus) resin (1.30 g) in benzene (CAUTION!) (250 mL) were heated at reflux in a Dean–Stark apparatus for 16 h. After cooling to rt, the reaction mixture was filtered, concentrated and the resulting residue dissolved in 2 M aqueous NaOH (40 mL). The reaction mixture was then heated at reflux for 2 h, cooled to rt, acidified to pH 1 with ice cold 6 M aqueous H_3PO_4 (25 mL) and rapidly extracted with EtOAc (4×20 mL). The combined organic extracts were then dried (Na_2SO_4), concentrated and the resulting residue purified by flash chromatography on silica gel (EtOAc/hexanes, 3:1) to provide **7f** (8.42 g, 65%): brown solid; mp 75–76°C; R_f 0.50 (EtOAc/hexanes, 3:1); IR (KBr) 3507, 2974, 1741, 1206, 1155, 911, 743, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (m, 1H), 3.95–3.83 (m, 2H), 1.75–1.65 (m, 1H), 1.58 (s, 3H), 1.45 (m, 1H), 1.31 (d, $J=6.1$ Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 176.2, 98.6, 69.5, 63.5, 31.9, 26.7, 22.0; high-resolution mass spectrum (EI) m/z 115.0760 [$(M-CO_2H)^+$; calcd for $C_6H_{11}O_2$ 115.0760].

4.3.2. 2-Carboxy-2-methyl-1,3-dioxane, 7e. (1.87 g, 73%): white solid; mp 94–95°C; R_f 0.65 (EtOAc/hexanes, 3:1); IR (KBr) 3501, 2924, 1735, 1208, 1153, 910, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.06–4.02 (m, 2H), 3.96–3.89 (m, 2H), 2.15–2.10 (m, 1H), 1.59 (s, 3H), 1.44–1.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.8, 98.3, 63.4, 26.1, 24.6; high-resolution mass spectrum (EI) m/z 101.0602 [$(M-CO_2H)^+$; calcd for $C_6H_{10}O_4$ 101.0602].

4.4. Representative procedure for the preparation of α-diazo ketones 2

4.4.1. 2-Diazoacetyl-2,5,5-trimethyl-1,3-dioxane, 2a. A solution of acid **7a** (500 mg, 2.8 mmol) and Et_3N (48 μL, 3.4 mmol) in anhydrous CH_2Cl_2 (10 mL) was cooled to −20°C and isobutyl chloroformate (38 μL, 3.0 mmol) was added dropwise via syringe. After stirring for 5 min, an ethereal solution of diazomethane (CAUTION!) (0.1 M, 43 mL, 4.3 mmol) was added via a flame-polished pipette and the reaction mixture allowed to warm to rt over 16 h. The mixture was then concentrated and the resulting residue purified by flash chromatography on silica gel (EtOAc/hexanes, 2:5) to provide **2a** (550 mg, 99%): yellow solid; mp 65–66°C; R_f 0.48 (EtOAc/hexanes, 2:5); IR (KBr) 2952, 2867, 2106, 1645, 1336, 1193, 909, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.73 (s, 1H), 3.52 (d, $J=11.1$ Hz, 2H), 3.49 (d, $J=11.1$ Hz, 2H), 1.45 (s, 3H), 1.18 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 100.4, 73.2 (2 C), 53.7, 29.7, 25.3, 22.6, 22.0; high-resolution mass spectrum (CI) m/z 199.1079 [$(M+H)^+$; calcd for $C_9H_{15}N_2O_3$ 199.1083].

4.4.2. *trans*-2-Diazoacetyl-*cis*-2,4,6-trimethyl-1,3-dioxane, 2b. (540 mg, 95%) yellow oil; R_f 0.28 (EtOAc/hexanes, 3:1); IR (film) 3123, 2973, 2934, 2106, 1646, 1330,

1199, 1175, 1109, 972, 911, 743, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.68 (s, 1H), 3.91–3.77 (m, 2H), 1.52–1.48 (m, 1H), 1.48 (s, 3H), 1.27–1.24 (m, 1H), 1.22 (d, $J=6.1$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 101.4, 68.7 (2 C), 53.4, 39.5, 26.9 (2 C), 21.9; high-resolution mass spectrum (CI) m/z 199.1078 [(M+H)$^+$; calcd for $C_{10}H_{17}N_2O_3$ 199.1083].

4.4.3. 2-Diazoacetyl-5,5-diethyl-2-methyl-1,3-dioxane, 2c. (660 mg, 87%): white solid; mp 70–71°C; R_f 0.38 (EtOAc/hexanes, 3:1); IR (KBr) 2965, 2875, 2106, 1647, 1460, 1336, 1196, 1087, 1030, 888, 832, 656; ^1H NMR (400 MHz, $CDCl_3$) δ 5.72 (s, 1H), 3.60 (d, $J=11.3$ Hz, 2H), 3.49 (d, $J=11.3$ Hz, 2H), 1.68 (q, $J=7.5$ Hz, 2H), 1.44 (s, 3H), 1.06 (q, $J=7.5$ Hz, 2H), 0.85 (t, $J=7.5$ Hz, 3H), 0.75 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.3, 100.3, 70.1 (2 C), 53.2, 34.2, 25.2, 24.1, 22.1, 7.4, 6.3; high-resolution mass spectrum (CI) m/z 227.1391 [(M+H)$^+$; calcd for $C_{11}H_{19}N_2O_3$ 227.1396].

4.4.4. 2-Diazoacetyl-8-methyl-7,9-dioxaspiro[4.5]decane, 2d. (670 mg, 99%): white solid; mp 62–63°C; R_f 0.17 (EtOAc/hexanes, 1:9); IR (KBr) 3123, 3084, 2953, 2864, 2106, 1647, 1336, 1194, 1032, 893, 831 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 5.73 (s, 1H), 3.61 (d, $J=11.0$ Hz, 2H), 3.52 (d, $J=11.0$ Hz, 2H), 1.79 (t, $J=6.9$ Hz, 2H), 1.68–1.60 (m, 2H), 1.58–1.51 (m, 2H), 1.42 (s, 3H), 1.11 (t, $J=6.9$ Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 194.3, 100.1, 71.6 (2 C), 53.4, 41.0, 33.9, 31.9, 25.3, 25.1, 24.4; high-resolution mass spectrum (CI) m/z 225.1259 [(M+H)$^+$; calcd for $C_{11}H_{17}N_2O_3$ 225.1239].

4.4.5. 2-Diazoacetyl-2-methyl-1,3-dioxane, 2e. (620 mg, 67%): yellow solid; mp 38–39°C; R_f 0.25 (EtOAc/hexanes, 2:5); IR (KBr) 3086, 2968, 2873, 2100, 1635, 1345, 1196, 1145, 976, 869, 821, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.73 (s, 1H), 3.97–3.83 (m, 4H), 2.09–1.98 (m, 2H), 1.42 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 194.1, 100.4, 62.6 (2 C), 53.4, 25.8, 24.5; high-resolution mass spectrum (CI) m/z 171.0769 [(M+H)$^+$; calcd for $C_7H_{11}N_2O_3$ 171.0770].

4.4.6. *trans*-2-Diazoacetyl-*cis*-2,4-dimethyl-1,3-dioxane, 2f. (690 mg, 99%): yellow solid; mp 33–34°C; R_f 0.31 (EtOAc/hexanes, 2:5); IR (KBr) 3124, 2972, 2106, 1652, 1335, 1198, 1045, 966, 913, 740, 681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.70 (s, 1H), 3.96–3.79 (m, 3H), 1.71–1.60 (m, 2H), 1.42 (s, 3H), 1.23 (d, $J=6.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 101.1, 68.8, 62.9, 53.5, 32.0, 26.8, 22.0; high-resolution mass spectrum (CI) m/z 185.0924 [(M+H)$^+$; calcd for $C_8H_{13}N_2O_3$ 185.0926].

4.4.7. *trans*-2-Diazoacetyl-2,5-dimethyl-5-nitro-1,3-dioxane, 2g. (340 mg, 62%): white solid; mp 64–65°C; R_f 0.59 (EtOAc/hexanes 2:5); IR (KBr) 3124, 2993, 2118, 1646, 1548, 1345, 1247, 1073, 887, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.72 (s, 1H), 4.31 (d, $J=12.5$ Hz, 2H), 4.01 (d, $J=12.5$ Hz, 2H), 1.72 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 100.3, 80.8, 66.9 (2C), 54.1, 22.0, 21.2; high-resolution mass spectrum (CI) m/z 247.1042 [(M+NH_4)$^+$; calcd for $C_8H_{15}N_4O_5$ 247.1042].

4.4.8. *cis*-2-Diazoacetyl-2,5-dimethyl-5-nitro-1,3-dioxane, 2h. (750 mg, 67%): yellow solid; mp 104–105°C; R_f 0.41 (EtOAc/hexanes, 2:5); IR (KBr) 3120, 2115, 1642, 1547, 1346, 1198, 1077, 1043, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.70 (s, 1H), 4.70 (d, $J=12.9$ Hz, 2H), 3.87 (d, $J=12.9$ Hz, 2H), 1.44 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 192.7, 100.8, 82.5, 67.3 (2 C), 54.3, 25.7, 19.7; high-resolution mass spectrum (CI) m/z 247.1040 [(M+NH_4)$^+$; calcd for $C_8H_{15}N_4O_5$ 247.1042].

4.5. Representative procedure for C–H insertion

4.5.1. Substrate 6a (Table 2, entry 1). To a flame-dried flask, under nitrogen, was added $Rh_2(OAc)_4$ (12.0 mg, 2 mol%) and anhydrous CH_2Cl_2 (48 mL). A solution of α-diazo ketone **2a** (250 mg, 1.28 mmol) in CH_2Cl_2 (8 mL) was then added to the reaction mixture over 20 h via syringe pump. The mixture was then filtered, concentrated and the resulting residue purified by flash chromatography on silica gel (EtOAc/hexanes, 1:9) to give ketone **3a** (110 mg, 52%) and enol ether **4a** (8 mg, 4%).

4.5.2. (±)-1,4,4-Trimethyl-2,8-dioxabicyclo[3.2.1]octan-7-one, 3a. Yellow oil; R_f 0.37 (EtOAc/hexanes, 2:5); IR (film) 2957, 2870, 1787, 1469, 1389, 1176, 1028, 921, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.20 (d, $J=7.5$ Hz, 1H), 3.62 (d, $J=12.1$ Hz, 1H), 3.47 (d, $J=12.1$ Hz, 1H), 2.60 (dd, $J=18.4$, 7.5 Hz, 1H), 2.40 (d, $J=18.4$ Hz, 1H), 1.37 (s, 3H), 1.33 (s, 3H), 0.76 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 211.5, 98.0, 80.4, 71.8, 37.6, 33.2, 24.7, 22.0, 18.2; high-resolution mass spectrum (CI) m/z 171.1015 [(M+H)$^+$; calcd for $C_9H_{15}O_3$ 171.1021].

4.5.3. (±)-1,4,4-Trimethyl-7-methylene-2,6,8-trioxabicyclo-[3.2.1]octane, 4a. White solid; readily sublimes; R_f 0.82 (EtOAc/hexanes, 2:5); IR (film) 3049, 2986, 2350, 1437, 895, 737, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.16 (s, 1H), 4.45 (d, $J=2.9$ Hz, 1H), 4.12 (d, $J=2.9$ Hz, 1H), 3.76 (d, $J=11.6$ Hz, 1H), 3.43 (d, $J=11.6$ Hz, 1H), 1.58 (s, 3H), 1.19 (s, 3H), 0.83 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 156.9, 107.7, 101.8, 80.2, 71.23, 35.2, 22.6, 21.4, 20.6; high-resolution mass spectrum (CI) m/z 188.1287 [(M+NH_4)$^+$; calcd for $C_9H_{18}NO_3$ 188.1287].

4.5.4. (±)-(1α,3α,5αβ)-1,3,5-Trimethyl-2,8-dioxabicyclo-[3.2.1]octan-7-one, 3b. (51 mg, 43%): colorless oil; R_f 0.05 (EtOAc/hexanes, 1:9); IR (film) 2972, 1762, 1445, 1375, 1170, 908, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.97–3.93 (m, 1H), 2.35 (s, 2H), 1.68 (d, $J=11.2$ Hz, 1H), 1.59 (dd, $J=11.2$, 3.8 Hz, 1H), 1.48 (s, 3H), 1.39 (s, 3H), 1.24 (d, $J=6.0$ Hz, 3H); ^{13}C (100 MHz, DMSO) δ 212.5, 99.7, 77.2, 67.1, 45.1, 42.1, 25.6, 21.8, 18.5; high-resolution mass spectrum (CI) m/z 171.1019 [(M+H)$^+$; calcd for $C_9H_{15}O_3$ 171.1021].

4.5.5. (±)-4,4-Diethyl-1-methyl-2,8-dioxabicyclo[3.2.1]-octan-7-one, 3c. (71 mg, 42%): colorless oil; R_f 0.27 (EtOAc/hexanes, 1:9); IR (film) 2968, 2877, 1767, 1463, 1384, 1089, 863, 802, 711 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.41 (d, $J=7.5$ Hz, 1H), 3.62 (d, $J=12.3$ Hz, 1H), 3.50 (d, $J=12.3$ Hz, 1H), 2.61 (dd, $J=18.2$, 7.5

Hz, 1H), 2.61 (d, $J=7.5$ Hz, 1H), 2.45 (d, $J=18.2$ Hz, 1H), 1.94 (q, $J=7.6$ Hz, 2H), 1.35 (s, 3H), 1.09 (q, $J=7.6$ Hz, 2H), 0.91 (t, $J=7.6$ Hz, 3H), 0.77 (t, $J=7.6$ Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 211.6, 128.3, 98.0, 69.4, 37.5, 37.1, 23.3, 22.8, 18.0, 7.5, 6.4; high-resolution mass spectrum (CI) m/z 199.1333 [(M+H)$^+$; calcd for $C_{11}H_{19}O_3$ 199.1334].

4.5.6. (±)-4,4-Diethyl-1-methyl-7-methylene-2,6,8-trioxabicyclo[3.2.1]octane, 4c. (20 mg, 12%) colorless oil; R_f 0.51 (EtOAc/hexanes, 1:9); IR (film) 2966, 2876, 1689, 1390, 1336, 1201, 1125, 958, 911, 855, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (s, 1H), 4.44 (d, $J=2.4$ Hz, 1H), 4.11 (d, $J=2.4$ Hz, 1H), 3.62 (d, $J=11.5$ Hz, 1H) 3.58 (d, $J=11.5$ Hz, 1H), 1.74 (q, $J=7.6$ Hz, 2H), 1.55 (s, 3H), 1.34 (q, $J=7.6$ Hz, 2H), 0.88 (t, $J=7.6$ Hz, 3H), 0.80 (t, $J=7.6$ Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 157.1, 105.8, 101.9, 80.0, 69.5, 40.0, 29.9, 22.8, 20.6, 7.8, 6.6; high-resolution mass spectrum (CI) m/z 199.1334 [(M+H)$^+$; calcd for $C_{11}H_{19}O_3$ 199.1334].

4.5.7. (±)-1-Methyl-2,8-dioxaspiro[4.5]bicyclo[3.2.1]-octan-7-one, 3d. (90 mg, 50%): white solid; mp 65–66°C; R_f 0.30 (EtOAc/hexanes, 2:5); IR (KBr) 2952, 2864, 1765, 1448, 1179, 1102, 864 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (d, $J=7.4$ Hz, 1H), 3.65 (d, $J=13.2$ Hz, 1H), 3.57 (d, $J=13.2$ Hz, 1H), 2.66 (dd, $J=18.2$, 7.4 Hz, 1H), 2.29 (d, $J=18.2$ Hz, 1H), 2.16–2.06 (m, 1H), 1.89–1.87 (m, 1H), 1.78–1.74 (m, 1H), 1.66–1.56 (m, 3H), 1.40 (s, 3H), 1.38–1.25 (m, 1H), 1.08–1.03 (m, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 211.6, 98.2, 80.1, 70.67, 45.0, 38.9, 36.5, 32.5, 25.6, 25.1, 18.2; high-resolution mass spectrum (CI) m/z 197.1162 [(M+H)$^+$; calcd for $C_{11}H_{17}O_3$ 197.1178].

4.5.8. (±)-4-Spiro[4.5]-1-methyl-7-methylene-2,6,8-trioxabicyclo[3.2.1]octane, 4d. (20 mg, 11%): colorless oil; R_f 0.66 (EtOAc/hexanes, 2:5); IR (film) 2955, 2866, 1688, 1453, 1369, 1333, 1198, 1122, 1022, 959, 910, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (s, 1H), 4.56 (d, $J=4.2$ Hz, 1H), 4.13 (d, $J=4.2$ Hz, 1H), 3.79 (d, $J=11.2$ Hz, 1H), 3.51 (d, $J=11.2$ Hz, 1H), 1.72–1.63 (m, 1H), 1.61–1.58 (m, 2H), 1.52 (s, 3H), 1.49–1.48 (m, 2H), 1.28–1.26 (m, 1H), 1.06–0.90 (m, 1H), 0.89–0.86 (m, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 157.2, 107.4, 101.7, 80.2, 70.6, 46.5, 34.0, 32.1, 25.6, 25.2, 20.6; high-resolution mass spectrum (CI) m/z 197.1165 [(M+H)$^+$; calcd for $C_{11}H_{17}O_3$ 197.1178].

4.5.9. (±)-1-Methyl-2,8-dioxabicyclo[3.2.1]octan-7-one, 2e. (70 mg, 44%): clear oil; R_f 0.33 (EtOAc/hexanes, 2:5); IR (film) 2977, 2939, 1760, 1383, 1181, 1092, 919, 842, 740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (m, 1H), 4.00–3.93 (m, 2H), 2.71 (dd, $J=18.3$, 7.8, Hz, 1H), 2.51–2.47 (m, 1H), 2.27 (d, $J=18.3$ Hz, 1H), 1.43 (m, 1H), 1.29 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 211.2, 98.4, 71.7, 60.9, 39.7, 29.3, 18.7; high-resolution mass spectrum (CI) m/z 143.0715 [(M+H)$^+$; calcd for $C_7H_{11}O_3$ 143.0708].

4.5.10. (±)-(1α,5αβ)-1,5-Dimethyl-2,8-dioxabicyclo[3.2.1]-octan-7-one/(1α,3αβ)-1,3-dimethyl-2,8-dioxabicyclo-[3.2.1]octan-7-one, 2f. Inseparable mixture (1:1, ^{1}H NMR) of C-4 and C-6 C–H insertion products (110 mg, 54%): colorless oil: R_f 0.20 (EtOAc/hexanes, 1:9); IR (film) 2936, 2344, 1754, 1445, 1376, 1173, 1102, 665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81–4.78 (m, 1H), 4.05–3.88 (m, 3H), 2.72 (dd, $J=17.9$, 7.5 Hz, 1H), 2.36–2.26 (m, 3H), 2.17–2.15 (m, 1H), 2.04–2.00 (m, 1H), 1.59–1.56 (m, 2H), 1.55 (s, 3H), 1.45 (s, 6H), 1.35 (d, $J=6.1$ Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 211.9, 211.4, 100.6, 98.5, 71.7, 66.7, 61.8, 45.8, 40.26, 37.1, 35.2, 26.5, 22.3, 18.8; high-resolution mass spectrum (CI) m/z 157.0875 [(M+H)$^+$; calcd for $C_8H_{13}O_3$ 157.0865].

4.5.11. (±)-(1α,3α,5α)-1,4-Dimethyl-4-nitro-2,8-dioxabicyclo[3.2.1]octan-7-one, 2g. (21 mg, 27%): colorless oil; R_f 0.42; (EtOAc/hexanes, 1:1); IR (film) 2934, 1767, 1536, 1387, 1178, 1082, 859, 804, 481 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (d, $J=7.6$ Hz, 1H), 4.20 (d, $J=12.8$ Hz, 1H), 4.10 (d, $J=12.8$ Hz, 1H), 2.85 (dd, $J=19.0$, 7.6 Hz, 1H), 2.28 (d, $J=19.0$ Hz, 1H), 2.03 (s, 3H), 1.42 (s, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 207.4, 98.8, 81.1, 76.0, 66.0, 38.2, 23.7, 17.5; high-resolution mass spectrum (CI) m/z 219.0971 [(M+NH$_4$)$^+$; calcd for $C_8H_{15}N_2O_5$ 219.0981].

4.5.12. (±)-(4-Benzyloxymethyl-1-methyl-7-oxo-2,8-dioxabicyclo[3.2.1]oct-4-yl)-carbamic acid benzyl ester, 8. (365 mg, 43%); colorless oil; R_f 0.65 (EtOAc/hexanes, 1:1); IR (film) 3352, 3030, 2936, 2874, 1767, 1716, 1526, 1453, 1384, 1250, 1180, 1073, 1028, 739, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.14 (m, 10H), 5.50 (s, 1H), 5.13 (d, $J=12.2$ Hz, 1H), 5.10 (d, $J=12.2$ Hz, 1H), 4.82 (d, $J=7.6$ Hz, 1H), 4.51 (d, $J=12.0$ Hz, 1H), 4.42 (d, $J=12.0$ Hz, 1H), 4.14 (d, $J=12.9$ Hz, 1H), 3.79 (d, $J=10.1$ Hz, 1H), 3.56 (d, $J=12.9$ Hz, 1H), 3.56 (d, $J=10.1$ Hz, 1H), 2.69 (dd, $J=7.6$, 18.7 Hz, 1H), 2.60 (d, $J=18.7$ Hz, 1H), 1.38 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 209.7, 155.4, 137.6, 136.4, [(128.8, 128.7, 128.4, 128.3, 127.9, (10 C)], 98.6, 75.4, 73.8, 68.0, 66.9, 65.2, 55.5, 37.7, 18.1; high-resolution mass spectrum (CI) m/z 412.17594 [(M+H)$^+$; calcd for $C_{23}H_{26}O_6N$, 412.17601].

4.6. Total synthesis of 7-episordidin, 13b

4.6.1. *trans*-2-Cyano-2-ethyl-*cis*-4,6-dimethyl-1,3-dioxane, 17. To a stirred solution of *meso*-2,4-propanediol 14 (650 mg, 6.25 mmol) and *p*-TsOH (25 mg, 0.13 mmol) in CH_2Cl_2 (40 mL) at rt was added triethyl orthopropionate (1.83 mL, 9.38 mmol) and the reaction stirred for 3 h. Trimethylsilyl cyanide (3.10 g, 31.25 mmol) (CAUTION!) and $BF_3{\cdot}Et_2O$ (159 μL, 1.27 mmol) were then sequentially added and the resulting mixture stirred for an additional 16 h at rt. The reaction was then quenched with powdered anhydrous K_2CO_3 (1.5 g), stirred for 20 min then filtered through a pad of Celite. The filtrate was then concentrated under reduced pressure to provide **17** (1.04 g, 99%). Analysis of this material by ^{1}H NMR spectroscopy indicated that it was of sufficient purity to allow direct submission to hydrolysis: yellow oil; IR (film) 3071, 2930, 2872, 2260, 1449, 1360, 1209, 1098, 922 cm^{-1}; ^{1}H

NMR (400 MHz) δ 4.15–4.12 (m, 2H), 1.90 (q, $J=7.4$ Hz, 2H), 1.60–1.57 (m, 1H), 1.28–1.26 (m, 1H), 1.22 (d, $J=8.7$ Hz, 6H), 1.07 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.1, 97.5, 70.2 (2 C), 39.1, 33.4, 21.0 (2 C), 7.2; high-resolution mass spectrum (CI) m/z 170.1182 [$(M+H)^+$; calcd for $C_9H_{16}NO_2$ 170.1181].

4.6.2. *trans*-2-Carboxyamide-2-ethyl-*cis*-4,6-dimethyl-1,3-dioxane, 18. A mixture of **17** (450 mg, 2.66 mmol), NaOH (1.06 g, 26.50 mmol) and aqueous H_2O_2 (30%, 812 μL, 26.50 mmol) in ethanol (35 mL) was heated at reflux for 3 h. The reaction mixture was then concentrated under reduced pressure to leave a yellow paste which was taken up in H_2O (10 mL), acidified to pH 1 with 5 M aqueous HCl then quickly extracted with CH_2Cl_2 (4×20 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated under reduced pressure to leave a white powder which was recrystallized from hexane to provide **18** (454 mg, 91%): colorless crystals; mp 118–119°C; R_f 0.32 (EtOAc/hexanes, 9:1); IR (KBr) 3324, 2972, 2934, 1682, 1385, 1200, 1171, 1112, 1001, 910, 742, 646 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (br s, 1H), 5.57 (br s, 1H), 3.93–3.86 (m, 2H), 1.77 (q, $J=7.5$ Hz, 2H), 1.52–1.49 (m, 1H), 1.29–1.26 (m, 1H), 1.24 (d, $J=8.6$ Hz, 6H), 0.98 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 101.2, 68.7 (2 C), 39.7, 33.6, 21.9 (2 C), 7.2; high-resolution mass spectrum (CI) m/z 188.1285 [$(M+H)^+$; calcd for $C_9H_{18}NO_3$ 188.1287].

4.6.3. *trans*-2-Carboxymethyl-2-ethyl-*cis*-4,6-dimethyl-1,3-dioxane, 15. A solution of amide **18** (250 mg, 1.33 mmol) and DMF–DMA (811 μL, 6.68 mmol) in anhydrous MeOH (5 mL) was placed in a pressure tube. The reaction mixture was then subjected to three cycles of freeze-thawing under nitrogen, sealed and heated at 110°C for 48 h during which time the reaction turned dark brown. After cooling to 0°C, the pressure tube was cautiously opened and the reaction mixture concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (EtOAc/hexanes, 1:4) to furnish **15** (260 mg, 96%): yellow oil; R_f 0.66 (EtOAc/hexanes, 1:4); IR (film) 2974, 1742, 1384, 1104, 1011, 816, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84–3.78 (m, 2H), 3.76 (s, 3H), 1.72 (q, $J=7.5$ Hz, 2H), 1.48–1.42 (m, 1H), 1.28–1.26 (m, 1H), 1.22 (d, $J=8.4$ Hz, 6H), 0.95 (t, $J=7.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 101.1, 68.7 (2 C), 52.3, 39.7, 32.8, 21.8 (2 C), 7.0; high-resolution mass spectrum (CI) m/z 203.1283 [$(M+H)^+$; calcd for $C_{10}H_{19}O_4$ 203.1290].

4.6.4. *trans*-2-Carboxy-2-ethyl-*cis*-4,6-dimethyl-1,3-dioxane. A solution of ester **15** (100 mg, 0.50 mmol) and NaOH (100 mg, 2.50 mmol) in THF (15 mL) and H_2O (15 mL) was heated at reflux for 16 h. The reaction mixture was then concentrated, cooled to 0°C, acidified to pH 1 with ice cold 5 M aqueous HCl (5 mL) and then rapidly extracted with EtOAc (4×15 mL). The combined extracts were then dried (Na_2SO_4) and concentrated under reduced pressure to provide the title compound (92 mg, 99%): white solid; mp 79–80°C; IR (KBr) 3521 3279, 2981, 1729, 1377, 1319, 1200, 1102, 1012, 717 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 3.94–3.86 (m, 2H), 1.86 (q, $J=7.5$ Hz, 2H), 1.53–1.49 (m, 1H), 1.28–1.26 (m, 1H), 1.25 (d, $J=8.4$ Hz, 6H), 0.98 (t, $J=7.5$ Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 176.6, 100.8, 69.1 (2 C), 39.6, 32.7, 21.8 (2 C), 7.0; high-resolution mass spectrum (CI) m/z 206.1394 [$(M+NH_4)^+$ calcd for $C_9H_{20}NO_4$ 206.1392].

4.6.5. *trans*-2-Diazoacetyl-2-ethyl-*cis*-2,4-dimethyl-1,3-dioxane, 19. A solution of the carboxylic acid prepared in Section 4.6.4 (150 mg, 0.79 mmol) and Et_3N (132 μL, 0.95 mmol) in anhydrous CH_2Cl_2 (10 mL) was cooled to −20°C and isobutyl chloroformate (112 μL, 0.83 mmol) then added dropwise via syringe. After stirring for 5 min, an ethereal solution of diazomethane (0.1 M, 12 mL, 1.20 mmol) (CAUTION!) was added via a flame-polished pipette and the reaction mixture allowed to warm to rt over 16 h. The mixture was then concentrated under reduced pressure (CAUTION!) and the resulting residue purified by flash chromatography on silica gel (EtOAc/hexanes, 1:9) to provide **19** (168 mg, 99%): yellow oil; R_f 0.56 (EtOAc/hexanes, 1:4); IR (film) 2975, 2937, 2132, 1899, 1340, 1277, 1114, 1007 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (s, 1H), 3.95–3.83 (m, 2H), 1.76 (q, $J=7.5$ Hz, 2H), 1.49–1.47 (m, 1H), 1.28–1.26 (m, 1H), 1.26 (d, $J=8.4$ Hz, 6H), 0.98 (t, $J=7.5$ Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 194.3, 101.4, 68.3 (2 C), 54.3, 39.6, 33.0, 21.9 (2 C), 7.0; high-resolution mass spectrum (CI) m/z 213.1239 [$(M+H)^+$; calcd for $C_{10}H_{17}N_2O_3$ 213.1239].

4.6.6. (1α,3α,5α,β)-1-Ethyl-3,5-dimethyl-2,8-dioxa-bicyclo[3.2.1]octan-7-one (20) and (1α,3α,5α,β)-1-ethyl-3,5-dimethyl-7-methylene-2,6,8-trioxa-bicyclo[3.2.1]octane, 21. A solution of **19** (1.85 g, 8.74 mmol) in anhydrous CH_2Cl_2 (30 mL) was added, via syringe pump, to a solution of $Rh_2(OAc)_4$ (77 mg, 2 mol%) in CH_2Cl_2 (570 mL) over 60 h. The reaction was filtered through Celite and concentrated under reduced pressure. The resulting residue was then purified by flash chromatography on silica gel (EtOAc/hexanes, 1:9) to give furanone **20** (938 mg, 58%) and enol ether **21** (450 mg, 28%). Data for **20**: colorless oil; R_f 0.46 (EtOAc/hexanes, 2:5); IR (film) 2976, 2936, 1764, 1380, 1274, 1179, 1132, 943, 793 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98–3.29 (m, 1H), 2.32 (d, $J=8.1$ Hz, 1H), 2.26 (d, $J=12.8$ Hz, 1H), 1.79–1.72 (m, 2H), 1.66–1.62 (m, 1H), 1.59 (dd, $J=9.5$, 3.9 Hz, 1H), 1.48 (s, 3H), 1.25 (d, $J=6.1$ Hz, 3H), 0.98 (t, $J=7.5$ Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 221.7, 102.5, 77.0, 67.6, 47.2, 43.3, 26.4, 25.5, 22.2, 7.1; high-resolution mass spectrum (CI) m/z 185.1170 [$(M+H)^+$; calcd for $C_{10}H_{17}O_3$ 185.1178]. Data for **21**: colorless oil; R_f 0.84 (EtOAc/hexanes, 2:5); IR (film) 2978, 2936, 1685, 1392, 1208, 1158, 1075, 1033, 974, 915, 821, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (d, $J=2.4$ Hz, 1H), 4.70–4.64 (m, 1H), 4.49 (d, $J=2.4$ Hz, 1H), 2.48–2.33 (m, 1H), 2.31–2.25 (m, 2H), 2.13–2.10 (m, 1H), 2.02 (s, 3H), 1.74 (d, $J=6.1$ Hz, 3H), 1.36 (t, $J=7.5$ Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 157.9, 107.5, 105.4, 79.2, 67.0, 42.3, 27.3, 23.3, 21.3, 7.7; high-resolution mass spectrum (CI) m/z 185.1173 [$(M+H)^+$; calcd for $C_{10}H_{17}O_3$ 185.1178].

4.6.7. (1α,3α,5α,β,7β)1-Ethyl-3,5,7-trimethyl-2,8-dioxa-bicyclo[3.2.1]octan-7-ol, 23. To a solution of MeMgI (1 M in Et_2O, 430 μl, 4.3 mmol) in THF (8 mL), at 0°C, was added a solution of **20** (150 mg, 0.815 mmol) in THF (2 mL). The reaction mixture was stirred for 3 h at 0°C then poured into saturated aqueous NH_4Cl (5 mL). The mixture was then extracted with pentane (5×5 mL) and the combined extracts dried (Na_2SO_4) and concentrated under reduced pressure to provide **23** (160 mg, 99%) which ^1H NMR spectroscopy indicated was of sufficient purity to be used in the following procedure: white powdery solid; R_f 0.30 (EtOAc/hexanes, 1:3); mp 79–80°C; IR (KBr) 3453, 2971, 2933, 1454, 1376, 1263, 1155, 1045, 948, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.31–4.25 (m, 1H), 2.49 (bs, 1H), 2.04 (d, $J=13.3$ Hz, 1H), 1.82 (d, $J=13.3$ Hz, 1H), 1.68–1.58 (m, 2H), 1.47 (apar.d, $J=7.5$ Hz, 2H), 1.33 (s, 3H), 1.29 (s, 3H), 1.25 (d, $J=6.0$ Hz, 3H), 1.01 (t, $J=7.5$ Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 106.5, 80.4, 77.7, 66.6, 51.1, 43.7, 28.2, 26.7, 26.3, 22.2, 7.5; high-resolution mass spectrum (CI) m/z 201.1488 [$(M+H)^+$; calcd for $C_{11}H_{21}O_3$ 201.1491].

4.6.8. (1α,3α,5α,β,7β)1-Ethyl-3,5,7-trimethyl-7-methyl-oxylate-2,8-dioxa-bicyclo[3.2.1]octane, 24. To a solution of **23** (9.0 mg, 0.045 mmol) in Et_2O (5 mL) was cooled to −78°C and *n*-BuLi (1.71 M in hexanes, 30 μL, 0.050 mmol) was dropwise via a syringe. After stirring for 10 min, methyl chlorooxoacetate (6.2 μL, 0.068 mmol) was added. The reaction was stirred for 1 h at −78°C and then for 2 h at rt before being poured into aqueous saturated $NaHCO_3$ (10 mL). This mixture was then extracted with CH_2Cl_2 (3×10 mL) and the extracts dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was then purified by flash chromatography on silica gel (EtOAc/hexanes, 1:3) to provide 24 (10 mg, 78%): white crystalline solid; R_f 0.33 (EtOAc/hexanes, 1:3); mp 58–60°C; IR (film) 2971, 2938, 1767, 1745, 1446, 1377, 1327, 1204, 1166, 964, 789 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.15–4.09 (m, 1H), 3.89 (s, 3H), 2.43 (d, $J=14.3$ Hz, 1H), 2.10 (d, $J=14.3$ Hz, 1H), 1.83–1.74 (m, 1H), 1.72–1.63 (m, 1H), 1.61 (s, 3H), 1.46–1.44 (m, 2H), 1.31 (s, 3H), 1.21 (d, $J=6.0$ Hz, 3H), 1.04 (t, $J=7.5$ Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 159.0, 157.6, 106.3, 90.3, 78.0, 66.1, 53.7, 48.6, 43.8, 27.2, 26.9, 24.5, 22.3, 7.9; high-resolution mass spectrum (CI) m/z 287.1496 [$(M+H)^+$; calcd for $C_{14}H_{23}O_6$ 287.1495].

4.6.9. (±)-7-Episordidin, 13b. A solution of **24** (75 mg, 0.26 mmol), Bu_3SnH (137 μL, 0.39 mmol) and AIBN (64 mg, 0.39 mmol) in anhydrous degassed benzene (10 mL) was purged with nitrogen and then heated at reflux for 16 h. The reaction mixture was then concentrated by distillation at atmospheric pressure and the resulting residue purified by radial chromatography on silica gel (2 mm plate, EtOAc/pentane, 1:20) to provide (±)-7-episordidin **13b** (21.3 mg, 45%): colorless oil; R_f 0.42 (Et_2O/hexanes, 1:9); IR (film) 2974, 2933, 2884, 1455, 1380, 1216, 1162, 1070, 962 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.10–4.05 (m, 1H), 2.25–2.22 (m, 1H), 1.99 (t, $J=12.5$ Hz, 1H), 1.75–1.62 (m, 1H), 1.57–1.49 (m, 1H), 1.49–1.41 (m, 2H), 1.40–1.37 (m, 1H), 1.32 (s, 3H), 1.18 (d, $J=6.1$ Hz, 3H), 1.09 (d, $J=7.2$ Hz, 3H), 0.93 (t, $J=7.5$ Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 107.6 (C1), 78.7 (C5), 65.6 (C3), 44.6 (C6), 42.4 (C4), 40.6 (C7), 29.1 (C8), 26.5 (C11), 22.2 (C10), 12.7 (C12), 7.9 (C9); GCMS (EI, 70 eV) 51, 57, 67, 83, 95, 100, 113, 142, 169, 184; high-resolution mass spectrum (CI) m/z 185.1545 [$(M+H)^+$; calcd for $C_{11}H_{21}O_2$ 185.1542].

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