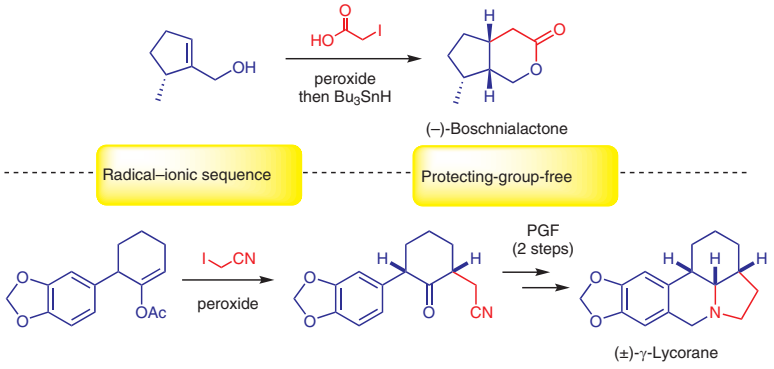
Synthesis A. Basante-Avendaño et al. Paper

A Free-Radical and Protecting-Group-Free Approach to (–)-Boschnialactone and γ-Lycorane

Alberto Basante-Avendaño ◊
Víctor E. Guerra-Ayala ◊
Alma Sánchez-Eleuterio
Alejandro Cordero-Vargas*

Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior s/n, Ciudad Universitaria, Coyoacán, 04510 Mexico City, Mexico
acordero@unam.mx

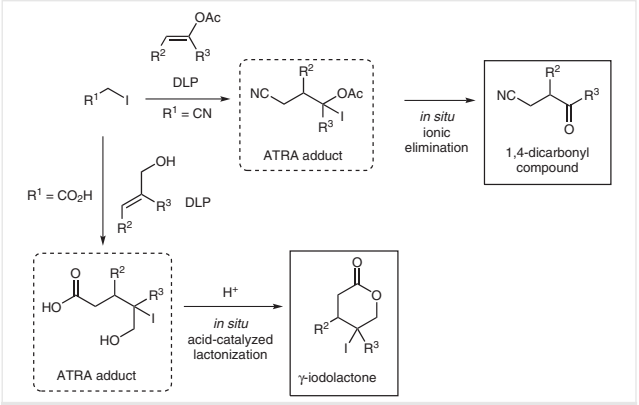
◊ Contributed equally to this work



Received: 14.12.2018
Accepted after revision: 16.01.2019
Published online: 27.02.2019
DOI: 10.1055/s-0037-1612248; Art ID: ss-2018-m0848-op

Abstract The protecting-group-free (PGF) and free-radical-based synthesis of two structurally different natural products, (–)-boschnialactone and γ-lycorane, is reported. The key step in both syntheses is a radical–ionic sequence for construction of the principal structure (a six-membered lactone and a 1,4-dicarbonyl compound, respectively), allowing short and rapid access to these natural products through a PGF route.

Key words radicals, protecting-group-free synthesis, atom-transfer radical addition, ATRA, boschnialactone, lycorane

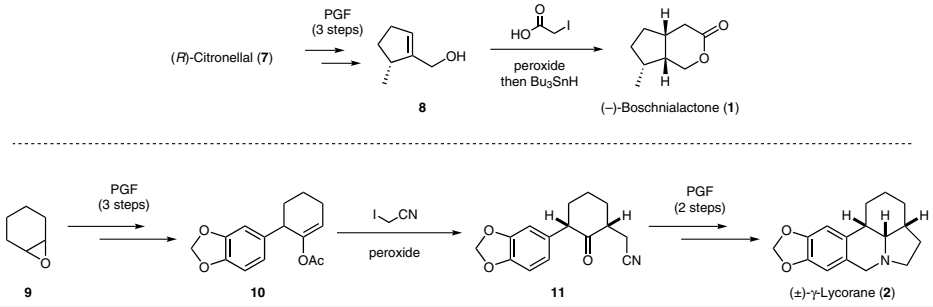


Scheme 1 Preparation of 1,4-dicarbonyl compounds and γ-iodolactones through ATRA–ionic sequences

Although protecting groups are crucial in synthesis, as Philip Kocieński has stated in his classic book,[1] the truth is that they have a tremendous ecological and economic cost that sometimes is not worth the expense. Consequently, many synthetic strategies to circumvent protecting groups have been reported.[2] In this regard, and due to the neutral character of free radicals, these reactive intermediates are the ideal partners in protecting-group-free (PGF) synthesis. In particular, atom transfer radical addition (ATRA) can provide suitable intermediates that can be transformed into useful molecules for the construction of complex natural products. For instance, either the transferred atom or group (halogen, usually) provides a new starting point for additional radical or ionic reactions. Accordingly, in recent years, our group has developed new radical–ionic sequences for the preparation of epoxides,[3] lactams,[4] 1,4-dicarbonyl compounds,[5] and iodolactones,[6] showcasing the usefulness of this strategy (Scheme 1). Now, by using these synthetic strategies, the total synthesis of (–)-boschnialactone (**1**) and (±)-γ-lycorane (**2**) is reported.

Boschnialactone (**1**), an iridoid monoterpene lactone isolated from *Boschniakia rossica* by Sakan and co-workers,[7] exhibits interesting insecticidal activities. A number of racemic[8] and asymmetric[9] syntheses of **1** have been reported, albeit to the best of our knowledge, with the exception of Nangia's approach,[9d] all employing protecting groups. On the other hand, γ-lycorane is a lycorine-type natural product belonging to the Amaryllidaceae alkaloids.[10] Although many of these alkaloids possess interesting biological activities, γ-lycorane apparently does not exhibit useful pharmaceutical properties. However, it is a popular synthetic target for structural reasons, and several racemic[11] and asymmetric[12] syntheses have been reported (Figure 1).

The strategy for the synthesis of compounds **1** and **2** is shown in Scheme 2. In both cases, a radical–ionic sequence would be the key step. For boschnialactone (**1**), a rapid assembly was envisioned by using our lactonization protocol[6]



Scheme 2 Strategy for the synthesis of **1** and **2**

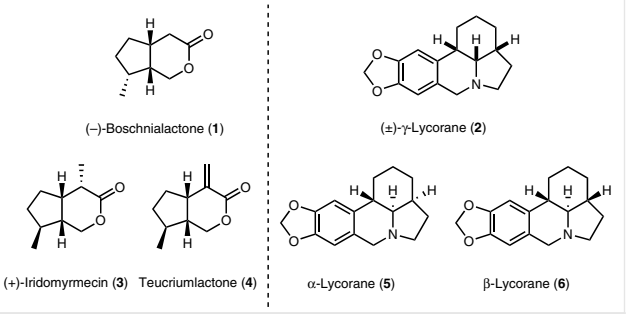
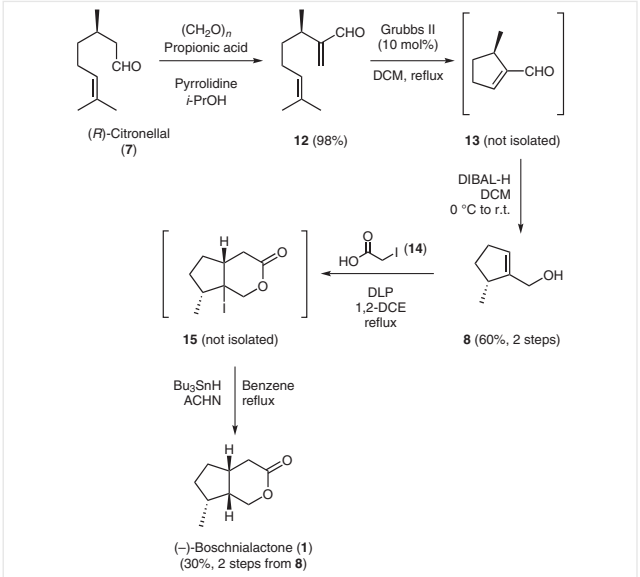


Figure 1 Representative iridoid monoterpenes and lycorine-type alkaloids

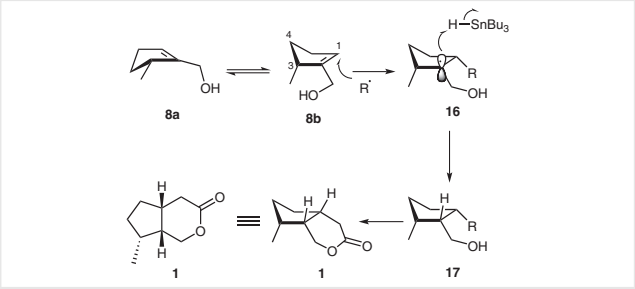
from iodoacetic acid and allylic alcohol **8**, which would be prepared by a PGF route from (*R*)-citronellal (**7**). The advanced intermediate **11** for the synthesis of γ-lycorane (**2**) can be prepared from a radical–ionic sequence[5] between enol acetate **10** and iodoacetonitrile. The former compound would be obtained in three steps from cyclohexene oxide (**9**) in a PGF fashion.

The synthesis of compound **1** commenced with the preparation of the respective radical acceptor **8** (Scheme 3). Several described routes were studied for obtaining alcohol **8**, in both racemic and enantiopure forms, however the best results were obtained by applying slightly modified conditions to those reported by Chavez and Jacobsen[9e] for aldehyde **13**. Methylenation of (*R*)-citronellal afforded compound **12** in 98% yield; then, RCM reaction with 10 mol% second-generation Grubbs catalyst rendered aldehyde **13**, which was directly reduced with DIBAL-H to the desired alcohol **8** in 60% yield for two steps. With radical acceptor **8** in hand, we proceeded to apply the key radical–ionic sequence. Treatment of a refluxing solution of **8** and iodoacetic acid (**14**, 2.4 equiv) in 1,2-dichloroethane (1,2-DCE) with lauroyl peroxide (DLP) generated unstable iodolactone **15**, which was treated in *one pot* with Bu_3SnH and 1,1′-azobis(cyclohexanecarbonitrile) (ACHN) after switching the solvent from 1,2-DCE to benzene. The crude reaction product revealed the presence of an inseparable 7:1 mixture of stereoisomers. The major isomer corresponded to (–)-boschnialactone (**1**) in 30% yield, whose chemical and spectroscopic data matched those reported previously.[9e]



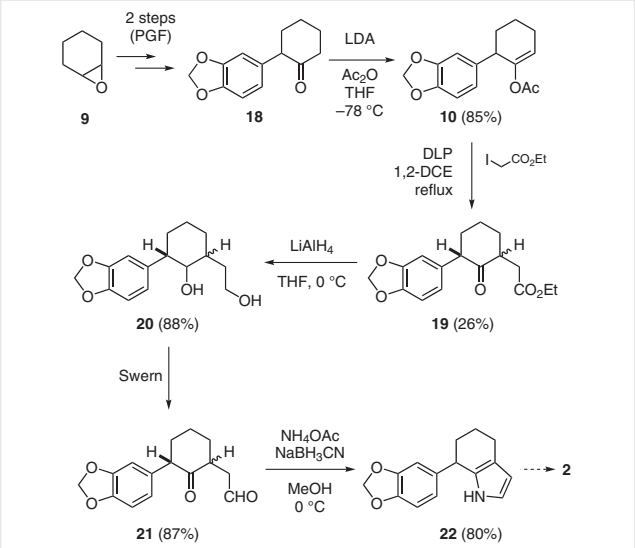
Scheme 3 PGF total synthesis of (–)-boschnialactone (**1**)

A plausible explanation for the observed *cis* selectivity is depicted in Scheme 4; low-energy conformer **8b** is attacked by radical R•, derived from iodoacetic acid, at the bottom face of the envelope conformation, in order to avoid steric interactions with C4. This gives rise to intermediate **16**, in which hydrogen-atom transfer by Bu_3SnH is carried out *anti* to substituents placed at C1 and C3, affording intermediate **17** with the desired stereochemistry. Subsequent *in situ* iodoacetic acid mediated lactonization furnishes the observed boschnialactone (**1**). Although attack of radical R• at conformer **8a** is also possible, lactone **1** was the only isolated compound, and these results are consistent with the observations by Field and Gallagher[13] for the hydroboration of 1,5-dimethylcyclopentene.



Scheme 4 Plausible explanation for the stereoselectivity for lactone **1**

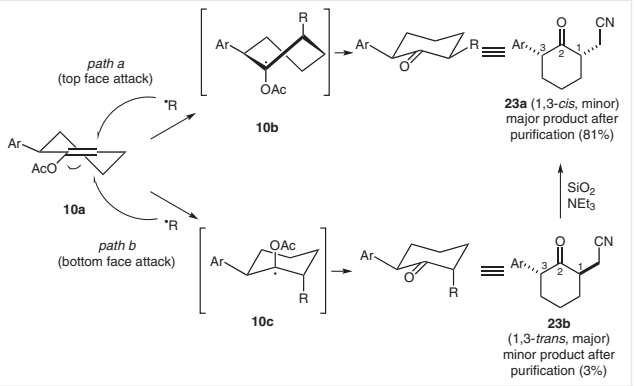
The preparation of enol acetate **10**, the radical acceptor for the synthesis of γ-lycorane (**2**), is depicted in Scheme 5. Known ketone **18**,[11g] prepared in two steps from cyclohexene oxide (**9**), was converted into enol acetate **10** by enolate formation with LDA and trapping with Ac_2O. It is worth mentioning that the acetate group is not a protecting group but is a way to switch the reactivity of the ketone moiety and to convert it into the required radical acceptor. With compound **10** in hand, the first approach to γ-lycorane was planned with the radical addition of ethyl iodoacetate to assemble **19**. However, the latter compound was isolated as an inseparable mixture of diastereoisomers (ca. 2:1) in low yield (26%); therefore, an adjustment of the oxidation level of the ester group was required before the introduction of the nitrogen atom. Reduction of both the ester and the ketone group followed by oxidation provided keto aldehyde **21**, which was submitted to reductive amination with ammonium acetate and sodium cyanoborohydride. Unexpectedly, the only recovered product was pyrrole **22** in 80% yield, even under different reaction conditions.



Scheme 5 Formal synthesis of γ-lycorane (**2**) *via* pyrrole **22**

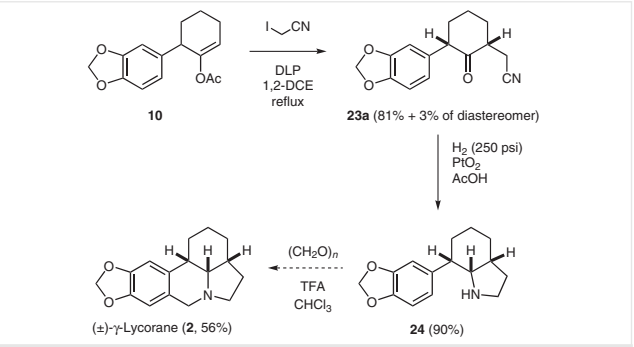
Although pyrrole **22** is known[11k] as a precursor of γ-lycorane (**2**), we looked for the possibility of performing a more straightforward and efficient route. In this regard, we anticipated that the addition of iodoacetonitrile to **10** would provide a compound with the correct carbon chain and the required nitrogen atom, which would eventually make part of the alkaloid skeleton through an intramolecular reductive amination. Compound **10** was then subjected to the previously employed conditions [DLP (1.2 equiv), added portionwise in refluxing 1,2-DCE] to afford keto nitrile **23** in 84% yield as a separable mixture of 1,3-*cis* (**23a**, 81%, major) and 1,3-*trans* (**23b**, 3%, minor) diastereoisomers. Although the stereochemistry of these compounds could not be established at this point, the further transformation of **23a** into γ-lycorane (see Scheme 7) allowed confirmation of the 1,3-*cis* relationship. Even though **23a** is the more stable stereoisomer due to the equatorial disposition of both substituents, the major compound observed by TLC during the reaction and by analysis of the crude ^{1}H NMR spectrum was **23b**. However, after column chromatography (silica gel, hexane/EtOAc/NEt_3), the only recovered product was **23a**, whereas **23b** could only be isolated, albeit in low yield (20%), when triethylamine was excluded from the eluent system. To confirm the assumption that **23b** was the major product which was then converted into the more stable **23a** during column chromatography, a solution of **23b** in hexane/ethyl acetate was stirred at room temperature with silica gel and NEt_3, and its complete transformation into **23a** was observed within 2 hours. In contrast, **23b** treated solely with either silica gel or NEt_3 did not show any change after several hours. These observations allowed us to conclude that **23b** is the major isomer formed in the reaction, but epimerization during column chromatography afforded the 1,3-*cis* compound **23a**. The stereoselectivity for the radical addition to enol acetate **10** can be explained according to the well-known conformation of cyclohexenes. Accordingly, compound **10** has the preferred half-chair conformation **10a**, with the aryl substituent in the equatorial position. Radical R• can thus approach from the top (*path a*) or the bottom (*path b*) face, leading in the former case to a less stable twisted boat conformation **10b**, which would eventually form 1,3-*cis* compound **23a**. On the contrary, attack of the radical from the bottom face (*path b*) would force the product to adopt an alternate, more stable chair conformation **10c** which, after transformation into the carbonyl compound, gives the 1,3-*trans* compound **23b** (Scheme 6).

With keto nitrile **23a** in hand, the next step consisted of the transformation of the nitrile moiety into a primary amine followed by an intramolecular reductive amination. A number of methods were tested, such as $NaBH_4/NiCl_2$, $LiAlH_4$, H_2/Raney Ni, H_2/Pd-C; however, incomplete reactions or a complex mixture of products was observed. After considerable experimentation, it was found that when **23a** was hydrogenated at 250 psi in the presence of PtO_2, both the nitrile reduction and the reductive amination occurred,



Scheme 6 Plausible explanation for the stereoselectivity for **23a**/**23b**

and the formation of **24** was accomplished in 90% yield. The spectroscopic data of **24** fully matched those reported,[11] and according to Bates and co-workers[11k] **24** can be directly transformed into γ-lycorane (**2**) through a Pictet–Spengler reaction (Scheme 7).



Scheme 7 Final steps for the formal synthesis of γ-lycorane (**2**)

In conclusion, we have reported two free-radical approaches to structurally different natural products: an iridoid, with a six-membered lactone as the main structure, and a lycorine-type alkaloid. Both syntheses rely on the use of a radical–ionic sequence as the key step, and because of the known tolerance of free radicals to unprotected functional groups, these steps were performed in a PGF fashion.

All operations were carried out under an inert atmosphere of nitrogen or argon gas using standard techniques. Anhydrous THF was obtained by distillation over sodium and benzophenone under an inert atmosphere. Column chromatography was performed using 70–230 mesh silica gel. All reagents and solvents were obtained from commercial suppliers and used without further purification. Melting points were obtained on a Melt-Temp II apparatus and are uncorrected. NMR spectra were measured with a JEOL Eclipse +300 or a Bruker Ascend (500 MHz) spectrometer, using $CDCl_3$ as solvent. Chemical shifts are in ppm (δ), relative to TMS. MS (DART) spectra were obtained on a JEOL DART AccuTOF JMS-T100CC instrument; signal values are expressed in mass/charge units (*m*/*z*).

3,7-Dimethyl-2-methyleneoct-6-enal (12)

To a solution of (*R*)-citronellal (**7**; 1 g, 6.48 mmol) and 37% aqueous formaldehyde solution (0.4 mL, 14.2 mmol) in *i*-PrOH (1.5 mL) at r.t. were slowly added propionic acid (0.12 mL, 1.62 mmol) and pyrrolidine (0.14 mL, 1.62 mmol). Then, the mixture was heated at 45 °C for 3 h until the starting material was completely consumed (monitored by TLC). The reaction was quenched with H_2O (10 mL) and the mixture extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, hexane) to afford aldehyde **12** as a colorless oil; yield: 1.06 g (98%). The spectroscopic data matched those reported by Pihko.[14]

$[\alpha]_D^{25}$ +5.30 (*c* 1, DCM).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.49 (s, 1 H), 6.19 (s, 1 H), 5.95 (s, 1 H), 5.04 (tt, *J* = 1.2, 7.2 Hz, 1 H), 2.67 (ddd, *J* = 13.8, 13.8, 6.9 Hz, 1 H), 1.96–1.85 (m, 2 H), 1.63 (s, 3 H), 1.53 (s, 3 H), 1.56–1.44 (m, 1 H), 1.40–1.31 (m, 1 H), 1.03 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.6, 155.5, 133.1, 131.7, 124.2, 35.6, 31.0, 25.8, 25.7, 19.6, 17.7.

(5-Methylcyclopent-1-en-1-yl)methanol (8)

A solution of aldehyde **12** (0.3 g, 1.8 mmol) in DCM (7 mL) under nitrogen atmosphere was transferred *via* cannula to a flask containing second-generation Grubbs catalyst (0.1 g, 0.12 mmol), followed by a second portion of DCM (7 mL) at r.t. The solution was heated at reflux under nitrogen for 24 h; then, the reaction mixture was filtered through a short pad of silica gel and washed with anhydrous DCM (15 mL) to remove the remaining solids of the Grubbs catalyst. The crude product solution was used in the next reaction without further purification due to the high volatility of aldehyde **13**.

To a solution of the crude aldehyde in DCM (29 mL) at 0 °C under nitrogen atmosphere was added 1 M DIBAL-H in DCM (3.6 mL, 3.6 mmol). The ice bath was removed, and the mixture was stirred for a further 40 min at r.t. The reaction was quenched with a saturated solution of Rochelle salt (5 mL) and the mixture stirred until a white jelly solid was formed. The reaction mixture was extracted with DCM (3 × 15 mL) and the combined organic layers were dried over Na_2SO_4. Removal of the solvent *in vacuo* yielded the crude alcohol which was purified by column chromatography (silica gel, DCM) to afford alcohol **8** as a pale yellow oil; yield: 0.121 g (60%, two steps).

$[\alpha]_D^{25}$ –7.14 (*c* 1, DCM).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.59–5.57 (m, 1 H), 4.21 (d, *J* = 13.8 Hz, 1 H), 4.14 (d, *J* = 13.8 Hz, 1 H), 2.78–2.66 (m, 1 H), 2.39–2.23 (m, 2 H), 2.19–2.08 (m, 1 H), 1.59 (brs, 1 H), 1.49–1.39 (m, 1 H), 1.03 (d, *J* = 13.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.5, 125.3, 60.9, 39.6, 33.1, 30.7, 19.4.

HRMS (DART): *m*/*z* $[M - OH]^+$ calcd for $C_7H_{12}O$: 95.08553; found: 95.08599.

(–)-Boschnialactone (1)

A solution of allylic alcohol **8** (0.3 g, 2.6 mmol) and iodoacetic acid (**14**; 1.15 g, 6.2 mmol) in 1,2-DCE (15 mL) was heated at reflux under nitrogen for 10 min. Then, DLP (20 mol%) was added every 1.5 h until the starting material was completely consumed (4 additions, 80 mol%; monitored by TLC). Then, the solvent was evaporated under re-

duced pressure and the residue dissolved in benzene (15 mL). To this solution, ACHN (0.87 g, 1 mmol) and Bu_3SnH (0.8 mL, 2.17 mmol) were sequentially added. The resulting mixture was heated at reflux under nitrogen for 2 h. When the starting material was completely consumed, the solvent was removed *in vacuo*, and the residue was purified by flash column chromatography (hexane/EtOAc, 30:1) to give **1** as an inseparable 7:1 mixture of diastereoisomers as a white solid; yield: 0.123 g (30%); mp 50–51 °C (Lit.[9e] 55–56 °C). The spectroscopic properties were identical in all aspects to those reported previously.[9e]

$[\alpha]_D^{25}$ –16.8 (*c* 1, DCM).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.21 (dd, *J* = 5.5, 11.4 Hz, 1 H), 4.11 (dd, *J* = 9.2, 11.7 Hz, 1 H), 2.66–2.54 (m, 2 H), 2.46–2.37 (m, 1 H), 2.35–2.25 (m, 1 H), 2.22–2.10 (m, 1 H), 1.94–1.79 (m, 2 H), 1.53–1.45 (m, 1 H), 1.39–1.29 (m, 1 H), 1.02 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.1, 67.7, 39.8, 37.5, 35.2, 35.0, 33.0, 32.9, 14.8.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_9H_{14}O_2$: 155.10720; found: 155.10790.

6-(Benzo[*d*][1,3]dioxol-5-yl)cyclohex-1-en-1-yl Acetate (10)

n-BuLi (2.5 M in hexanes, 1.46 mL, 3.67 mmol) was slowly added to a solution of diisopropylamine (0.54 mL, 3.85 mmol) in THF (10.5 mL) at 0 °C. The resulting solution was cooled at –78 °C and stirred for 30 min. Then, a solution of ketone **18** (400 mg, 1.83 mmol) in THF (8 mL) was transferred to the reaction flask, and the mixture was stirred for 30 min; then, the reaction was quenched with acetic anhydride (0.612 mL, 5.49 mmol) and the mixture allowed to stir for a further 30 min. The solvent was evaporated under reduced pressure, and the residue was partitioned between H_2O and EtOAc, and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexane/EtOAc/NEt_3, 15:1:0.1) afforded compound **10** as a white solid; yield: 405 mg (85%); mp 50–53 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.73–6.63 (m, 3 H), 5.90 (s, 2 H), 5.58 (t, *J* = 3.6 Hz 1 H), 3.67–3.60 (m, 1 H), 2.23–2.16 (m, 2 H), 2.12–2.01 (m, 1 H), 1.85 (s, 3 H), 1.72–1.55 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.4, 148.6, 147.6, 146.1, 136.5, 121.4, 116.6, 108.5, 108.0, 100.9, 43.0, 33.0, 24.0, 21.0, 19.3.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{16}O_4$: 261.11268; found: 261.11270.

Ethyl 2-(3-(Benzo[*d*][1,3]dioxol-5-yl)-2-oxocyclohexyl)acetate (19)

A solution of enol acetate **10** (150 mg, 0.58 mmol) and ethyl iodoacetate (204 µL, 1.73 mmol) in 1,2-DCE (5.8 mL) was refluxed under nitrogen for 10 min. Then, DLP was added portionwise (69.4 mg, 0.174 mmol) every hour until the complete consumption of starting material (monitored by TLC). The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography (silica gel, hexane/EtOAc/NEt_3, 20:1:0.1) to afford compound **19** as a mixture of diastereoisomers; yield: 46 mg (26%). Only the *cis* stereoisomer could be isolated as a single diastereoisomer for characterization purposes. The spectroscopic data matched those reported by Zhou and co-workers.[12g]

White solid; mp 83–85 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.81–6.69 (m, 3 H), 5.95 (s, 2 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 3.73 (t, *J* = 4.6 Hz, 1 H), 3.00 (m, 1 H), 2.75 (dd, *J* = 7.8, 16.4 Hz, 1 H), 2.54–2.45 (m, 1 H), 2.35 (t, *J* = 7.5 Hz, 2 H), 2.20 (dd, *J* = 6.0, 16.5 Hz, *J* = 7.7 Hz, 1 H), 2.10–1.99 (m, 2 H), 1.81–1.70 (m, 1 H), 1.24 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.6, 172.3, 147.6, 146.5, 132.3, 120.5, 108.6, 107.9, 101.2, 60.6, 53.8, 40.3, 33.7, 31.1, 21.0 14.3.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{20}O_5$: 305.13890; found: 305.14026.

2-(Benzo[*d*][1,3]dioxol-5-yl)-6-(2-hydroxyethyl)cyclohexan-1-ol (20)

To a solution of ester **19** (350 mg, 1.15 mmol) in THF (2.3 mL) at 0 °C was added $LiAlH_4$ (261.9 mg, 6.9 mmol). After 10 min at 0 °C, the reaction mixture was allowed to warm to r.t. and stirring was continued until starting material was totally consumed (TLC). The reaction was quenched by careful addition of 10% aqueous NaOH solution until pH 7. The mixture was filtered over Celite and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by column chromatography (silica gel, hexane/EtOAc, 15:1) afforded compound **20** (colorless oil) as a separable mixture of diastereoisomers; combined yield: 263.4 mg (88%).

Diastereoisomer I

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.77 (d, *J* = 7.9 Hz, 1 H), 6.75 (d, *J* = 1.6 Hz, 1 H), 6.70 (dd, *J* = 1.6, 7.9 Hz, 1 H), 5.94 (s, 2 H), 3.79–3.73 (m, 1 H), 3.68–3.59 (m, 1 H), 3.30 (t, *J* = 9.7 Hz, 1 H), 2.42 (ddd, *J* = 3.5, 10.0, 13.2 Hz, 1 H), 1.89–1.72 (m, 4 H), 1.67–1.51 (m, 4 H), 1.49–1.37 (m, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 148.3, 146.7, 136.8, 121.3, 108.6, 107.9, 101.1, 78.8, 62.0, 52.6, 43.2, 38.5, 33.6, 33.1, 25.9.

Diastereoisomer II

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.79–6.76 (m, 2 H), 6.71 (dd, *J* = 1.4, 8.0 Hz, 1 H), 5.93 (s, 2 H), 3.84 (s, 1 H), 3.78–3.66 (m, 2 H), 2.68 (dt, *J* = 2.8, 12.9 Hz, 1 H), 1.95–1.86 (m, 2 H), 1.80–1.71 (m, 3 H), 1.68–1.57 (m, 3 H), 1.48–1.46 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 147.9, 146.3, 137.9, 120.6, 108.5, 108.4, 101.0, 73.5, 60.4, 48.6, 39.7, 36.4, 26.1, 25.6, 24.6.

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{20}O_4$: 265.14398; found: 265.14490.

2-(3-(Benzo[*d*][1,3]dioxol-5-yl)-2-oxocyclohexyl)acetaldehyde (21)

To a solution of oxalyl chloride (0.39 mL, 4.6 mmol) in DCM (5.8 mL) at –78 °C was added DMSO (0.65 mL, 9.2 mmol) and the resulting solution was stirred for 30 min. To this solution was transferred, *via* cannula, a solution of diol **20** (278 mg, 1.05 mmol) in DCM (5.8 mL). After 90 min at –78 °C, NEt_3 (2.6 mL, 18.4 mmol) was added and the mixture stirred for a further 30 min. The reaction mixture was allowed to warm to r.t. and concentrated under reduced pressure. The residue was partitioned between H_2O and DCM and extracted with DCM (3 × 20 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. After column chromatography (silica gel, hexane/EtOAc, 15:1), **21** was obtained as a separable mixture of diastereoisomers (2:1); combined yield: 238 mg (87%).

Diastereoisomer I

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.77 (t, *J* = 0.97 Hz, 1 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 6.76 (m, 1 H), 6.70 (ddd, *J* = 1.0, 1.8, 8.0 Hz, 1 H), 5.95 (s, 2 H), 3.77–3.70 (m, 1 H), 3.15–3.03 (m, 1 H), 2.92 (ddd, *J* = 1.1, 7.6, 17.6 Hz, 1 H), 2.58–2.47 (m, 1 H), 2.30 (ddd, *J* = 0.9, 5.2, 17.7 Hz, 1 H), 2.11–1.88 (m, 4 H), 1.81–1.71 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.40, 200.77, 147.66, 146.63, 132.16, 121.78, 109.22, 108.23, 101.04, 57.26, 46.03, 43.82, 36.44, 34.88, 25.67.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}O_4$: 261.11268; found: 261.11368.

Diastereoisomer II

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.79 (t, *J* = 1.0 Hz, 1 H), 6.76 (d, *J* = 7.9 Hz, 1 H), 6.63 (d, *J* = 1.7 Hz, 1 H), 6.56 (ddd, *J* = 0.3, 1.7, 7.9 Hz, 1 H), 5.92 (s, 2 H), 3.68–3.58 (m, 1 H), 3.19–3.07 (m, 1 H), 2.99 (dd, *J* = 1.1, 7.6 Hz, 1 H), 2.30 (ddd, *J* = 0.8, 4.9, 17.6 Hz, 1 H), 2.35–2.17 (m, 2 H), 2.06–1.87 (m, 4 H).

7-(Benzo[*d*][1,3]dioxol-5-yl)-4,5,6,7-tetrahydro-1*H*-indole (22)

To a solution of **21** (50 mg, 0.19 mmol) in MeOH (4 mL) at 0 °C were added ammonium acetate (30 mg, 0.38 mmol) and 4 Å molecular sieves (50 mg). After stirring for 2 h at 0 °C, MeOH was evaporated off from the reaction flask and the residue was partitioned between H_2O and EtOAc. The mixture was extracted with EtOAc (3 × 10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. After column chromatography (silica gel, hexane/EtOAc, 15:1), **22** was obtained as a reddish oil; yield: 37 mg (80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (br s, 1 H), 6.74 (d, *J* = 8.5 Hz, 1 H), 6.65–6.60 (m, 3 H), 6.01 (t, *J* = 2.6 Hz, 1 H), 5.92 (s, 2 H), 3.91 (t, *J* = 6.7 Hz, 1 H), 2.63–2.59 (m, 2 H), 2.18–2.10 (m, 1 H), 1.95–1.85 (m, 1 H), 1.78–1.67 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.9, 146.3, 139.2, 129.0, 121.2, 118.4, 116.5, 108.6, 108.5, 107.2, 101.0, 41.5, 34.5, 23.1, 22.7.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}NO_2$: 242.11810; found: 242.11773.

2-(3-(Benzo[*d*][1,3]dioxol-5-yl)-2-oxocyclohexyl)acetonitrile (23)

A solution of enol acetate **10** (150 mg, 0.58 mmol) and iodoacetonitrile (83 µL, 1.15 mmol) in 1,2-DCE (5.8 mL) was refluxed under nitrogen for 10 min. Then, DLP was added portionwise (69.4 mg, 0.174 mmol) every hour until the complete consumption of starting material (monitored by TLC). The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography (silica gel, hexane/EtOAc/NEt_3, 20:1:0.1) to afford compound **23** as a mixture of diastereoisomers (24:1); combined yield: 124 mg (84%).

***cis*-Diastereoisomer 23a**

White solid; mp 106–109 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.77 (d, *J* = 7.9 Hz, 1 H), 6.62 (d, *J* = 1.7 Hz, 1 H), 6.56 (dd, *J* = 1.7, 7.9 Hz, 1 H), 5.93 (s, 2 H), 3.58 (dd, *J* = 5.4, 12.3 Hz, 1 H), 2.88–2.80 (m, 1 H), 2.71 (dd, *J* = 5.0, 17.1 Hz, 1 H), 2.49 (ddd, *J* = 2.4, 4.2, 9.9 Hz, 1 H), 2.43 (dd, *J* = 8.2, 17.1 Hz, 1 H), 2.34–2.29 (m, 1 H), 2.10–2.04 (m, 1 H), 1.97–1.91 (m, 2 H), 1.68–1.58 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.4, 147.8, 146.8, 131.4, 121.8, 118.6, 109.1, 108.3, 101.1, 57.2, 47.4, 36.3, 34.3, 25.2, 18.1.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}NO_3$: 258.11302; found: 258.11413.

***trans*-Diastereoisomer 23b**

Yellowish solid; mp 110–113 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.79 (d, *J* = 8.0 Hz, 1 H), 6.73–6.70 (m, 1 H), 6.69–6.64 (m, 1 H), 5.97–5.94 (m, 2 H), 3.80–3.75 (m, 1 H), 2.79 (ddt, *J* = 5.3, 7.9, 10.6 Hz, 1 H), 2.64 (dd, *J* = 17.0, 5.1 Hz, 1 H), 2.60–2.52 (m, 1 H), 2.39 (dd, *J* = 8.1, 17.0 Hz, 1 H), 2.34–2.23 (m, 1 H), 2.11–1.91 (m, 2 H), 1.89–1.80 (m, 1 H), 1.67–1.52 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.4, 148.5, 146.8, 130.4, 120.2, 118.5, 108.9, 107.5, 101.3, 53.4, 43.7, 33.3, 30.1, 20.8, 18.1.

(3a*R,7*S**,7a*S**)-7-(Benzo[*d*][1,3]dioxol-5-yl)octahydro-1*H*-indole (24)**

A mixture of nitrile **23a** (66 mg, 0.26 mmol, 1 equiv) and PtO_2 (19.8 mg, 30% w/w) in glacial acetic acid (3 mL) in a Fisher–Porter apparatus was stirred under hydrogen atmosphere (250 psi) at r.t. for 24 h. A solution of 2 M NaOH (20 mL) was added and the reaction mixture was extracted with DCM (3 × 20 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by column chromatography (silica gel, $CHCl_3$/MeOH/NEt_3, 9:1:0.1) to afford compound **24** as a yellow oil; yield: 56.6 mg (90%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.82 (s, 1 H), 6.74 (brs, 2 H), 5.91 (s, 2 H), 3.23 (t, *J* = 3.8 Hz, 1 H), 3.17–3.08 (m, 1 H), 2.93–2.86 (m, 2 H), 2.12–2.05 (m, 1 H), 1.98–1.85 (m, 3 H), 1.65–1.50 (m, 3 H), 1.34–1.25 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.7, 146.0, 138.4, 120.4, 108.3, 108.2, 100.9, 63.6, 44.3, 43.3, 38.9, 31.3, 27.4, 25.8, 24.9.

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}NO_2$: 246.14940; found: 246.14854.

Funding Information

Dirección General de Asuntos del Personal Académico, Universidad Nacional Autónoma de México (DGAPA-UNAM) for project number IN205318 and for a postdoctoral fellowship for A.S.-E. Consejo Nacional de Ciencia y Tecnología (CONACYT) for grants numbers 767928 (A.B.-A.) and 620665 (V.E.G.-A.).

Acknowledgment

The authors thank Angeles Peña-González, Elizabeth Huerta-Salazar, Beatriz Quiroz, and Carmen García-González for technical support (NMR and MS). We also thank Prof. Fernando Sartillo-Piscil (BUAP) and Prof. Marcos Hernández-Rodríguez (UNAM) for helpful suggestions during the preparation of the manuscript.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1612248.

References

(1) Kocieński, P. J. *Protecting Groups, 2nd ed*; Thieme: Stuttgart, **2000**.
(2) *Protecting-Group-Free Organic Synthesis*; Fernandes, R. A., Ed.; Wiley: Hoboken, NJ, **2018**.
(3) Peralta-Hernández, E.; Cortezano-Arellano, O.; Cordero-Vargas, A. *Tetrahedron Lett.* **2011**, *52*, 6899.
(4) Morales-Chamorro, M.; Meza-González, J.; Cordero-Vargas, A. *Tetrahedron Lett.* **2015**, *56*, 4892.
(5) Peralta-Hernández, E.; Blé-González, E. A.; Gracia-Medrano-Bravo, V. A.; Cordero-Vargas, A. *Tetrahedron* **2015**, *71*, 2234.
(6) León-Rayo, D. F.; Morales-Chamorro, M.; Cordero-Vargas, A. *Eur. J. Org. Chem.* **2016**, 1739.
(7) Sakan, T.; Murai, F.; Hayashi, Y.; Honda, Y.; Shono, T.; Nakajima, M.; Kato, M. *Tetrahedron* **1967**, *23*, 4635.
(8) (a) Callant, P.; Storme, P.; Van der Eycken, E.; Vanderwalle, M. *Tetrahedron Lett.* **1983**, *24*, 5797. (b) Storme, P.; Quaeghebeur, L.; Vandewalle, M. *Bull. Soc. Chim. Belg.* **1984**, *93*, 999. (c) Caille, C. J.; Tabyaoui, B.; Guilard, R. *Synth. Commun.* **1985**, *15*, 669. (d) Wang, T.-F.; Yang, C.-F. *J. Chem. Soc., Chem. Commun.* **1989**, 1876. (e) Hanquet, B.; Tabyaoui, B.; Caille, J.-C.; Farner, M.; Guilard, R. *Can. J. Chem.* **1990**, *68*, 620. (f) Chiu, J.-Y.; Chiu, C.-T.; Chang, N.-C. *J. Chin. Chem. Soc.* **1997**, *44*, 59. (g) Chang, M.-Y.; Lin, C.-H.; Lee, A.-Y.; Tai, H.-M.; Chang, N.-C. *J. Chin. Chem. Soc.* **1999**, *46*, 205. (h) Taniguchi, T.; Goto, Y.; Ogasawa, K. *Synlett* **1997**, 707.
(9) (a) Arai, Y.; Kawanami, S.; Koizumi, T. *Chem. Lett.* **1990**, 1585. (b) Arai, Y.; Kawanami, S.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2969. (c) Tanaka, D.; Yoshino, T.; Kuono, I.; Miyashita, M.; Irie, H. *Tetrahedron* **1993**, *49*, 10253. (d) Nangia, A.; Prasuna, G.; Rao, B. *Tetrahedron Lett.* **1994**, *35*, 3755. (e) Chavez, D. E.; Jacobsen, E. N. *Org. Lett.* **2003**, *5*, 2563. (f) Inoue, T.; Kitigawa, O.; Saito, A.; Taguchi, T. *J. Org. Chem.* **1997**, *62*, 7384.
(10) Kotera, K. *Tetrahedron* **1961**, *12*, 248.
(11) (a) Umezawa, B.; Hochino, O.; Sawaki, S.; Sato, S.; Numao, N. *J. Org. Chem.* **1977**, *42*, 4272. (b) Bäckvall, J.-E.; Andersson, P. G.; Stone, G. B.; Gogoll, A. *J. Org. Chem.* **1991**, *56*, 2988. (c) Banwell, M. G.; Wu, A. W. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2671. (d) Cossy, J.; Tresnard, L.; Gómez-Pardo, D. *Tetrahedron Lett.* **1999**, *40*, 1125. (e) Cassayre, J.; Zard, S. Z. *Synthesis* **1999**, 501. (f) Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2001**, *66*, 1716. (g) Gao, S.; Tu, Y. Q.; Song, Z.; Wang, A.; Fan, X.; Jiang, Y. *J. Org. Chem.* **2005**, *70*, 6523. (h) Huntley, R. J.; Funk, R. L. *Tetrahedron Lett.* **2011**, *52*, 6671. (i) Conner, E. S.; Crocker, K. E.; Fernando, R. G.; Froncsek, F. R.; Stanley, G. G.; Ragains, J. R. *Org. Lett.* **2013**, *15*, 5558. (j) Liu, D.; Ai, L.; Zhao, A.; Chen, J.; Zhang, H.; Liu, J. *Org. Biomol. Chem.* **2014**, *12*, 3191. (k) Doan, B. N. D.; Tan, X. Y.; Ang, C. M.; Bates, R. W. *Synthesis* **2017**, *49*, 4711. (l) Monaco, A.; Szulc, B. R.; Rao, Z. X.; Barniol-Xicota, M.; Sehailia, M.; Borges, B. M. A.; Hilton, S. T. *Chem. Eur. J.* **2017**, *23*, 4750. (m) Ho, G. M.; Li, Y.-J. *Asian J. Org. Chem.* **2018**, *7*, 145. (n) Osornio, Y. M.; Miranda, L. D. *Rev. Soc. Quim. Mex.* **2004**, *48*, 288.
(12) (a) Yoshizaki, H.; Satoh, H.; Sato, Y.; Nukui, S.; Shibasaki, M.; Mori, M. *J. Org. Chem.* **1995**, *60*, 2016. (b) Ikeda, M.; Ohtani, S.; Sato, T.; Ishibashi, H. *Synthesis* **1998**, 1803. (c) Dong, L.; Xu, Y.-J.; Cun, L.-F.; Cui, X.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2005**, *7*, 4285. (d) Dong, L.; Xu, Y.-J.; Yuan, W.-C.; Cui, X.; Cun, L.-F.; Gong, L.-Z. *Eur. J. Org. Chem.* **2006**, 4093. (e) Chapsal, B. D.; Ojima, I. *Org. Lett.* **2006**, *8*, 1395. (f) El Bialy, S. A. A. *Nat. Prod. Res.* **2008**, *22*, 1176. (g) Liu, C.; Xie, J.-H.; Li, Y.-L.; Chen, J.-Q.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2013**, *52*, 593.
(13) Field, L. D.; Gallagher, S. P. *Tetrahedron Lett.* **1985**, *26*, 6125.
(14) Erikkilä, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538.