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*0000-0003-1549-5977
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

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

Although protecting groups are crucial in synthesis, as Philip Kocięński 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 racemic8 and asymmetric9 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 racemic11 and asymmetric12 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 protocol6

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

© Georg Thieme Verlag Stuttgart · New York — Synthesis 2019, 51, A–G
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 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 Jacobsen5e for aldehyde 13. Methylation 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 Bu₃SnH and 1,1′-azobis(cyclohexane carbonitrile) (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.5e

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 Bu₃SnH 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 Gallagher13 for the hydroboration of 1,5-dimethylcyclopentene.
The preparation of enol acetate 10, the radical acceptor for the synthesis of γ-lycorane (2), is depicted in Scheme 5. Known ketone 18,18 prepared in two steps from cyclohexene oxide (9), was converted into enol acetate 10 by enolate formation with LDA and trapping with Ac₂O. 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 20, 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.

Although pyrrole 22 is known11 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 ¹H NMR spectrum was 23b. However, after column chromatography (silica gel, hexane/EtOAc/NEt₃), 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 NEt₃, and its complete transformation into 23a was observed within 2 hours. In contrast, 23b treated solely with either silica gel or NEt₃ 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 NaBH₄/NiCl₂, LiAlH₄, H₂/Raney Ni, H₂/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 PtO₂, both the nitrile reduction and the reductive amination occurred,

© Georg Thieme Verlag Stuttgart · New York — Synthesis 2019, 51, A–G
and the formation of 24 was accomplished in 90% yield. The spectroscopic data of 24 fully matched those reported, and according to Bates and co-workers, 24 can be directly transformed into γ-lycorane (2) through a Pictet–Spengler reaction (Scheme 7).

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 CDCl₃ 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 H₂O (10 mL) and the mixture extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried with Na₂SO₄, 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.

[α]D²⁵ +5.30 (c 1, DCM).

1H NMR (300 MHz, CDCl₃): 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).

13C NMR (75 MHz, CDCl₃): 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 (1.8 mL, 1.8 mmol). Then, the mixture was heated to reflux for another 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 precipitate formed. The mixture was filtered and the solid washed with anhydrous DCM (3 × 15 mL). Removal of the solvent in vacuo yielded the crude product 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).

[α]D²⁵ -7.14 (c 1, DCM).

1H NMR (300 MHz, CDCl₃): 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), 2.78–2.23 (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).

13C NMR (75 MHz, CDCl₃): δ = 148.5, 125.3, 60.9, 39.6, 33.1, 30.7, 19.4.

(–)-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 Bu₃SnH (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 afford compound reduced pressure and the residue purified by column chromatography (hexane/EtOAc, 20:1:0.1) 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. ² 55–56 °C). The spectroscopic properties were identical in all aspects to those reported previously.²e

1H NMR (400 MHz, CDCl₃): δ = 6.21–6.69 (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).

13C NMR (75 MHz, CDCl₃): 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 C₁₇H₂₀O₅: 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 LiAlH₄ (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 Na₂SO₄, 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

1H NMR (300 MHz, CDCl₃): δ = 6.77 (dd, 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 (dd, J = 3.5, 10.0, 13.2 Hz, 1 H), 1.89–1.72 (m, 4 H), 1.67–1.51 (m, 14 H), 1.49–1.37 (m, 2 H).

13C NMR (126 MHz, CDCl₃): 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

1H NMR (300 MHz, CDCl₃): 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).

13C NMR (126 MHz, CDCl₃): 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.


2-(3-Benzod[d][1,3]dioxol-5-yl)-2-oxocyclohexyl)acetate (21)

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, NET₃ (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 H₂O and DCM and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo.

© Georg Thieme Verlag Stuttgart · New York — Synthesis 2019, 51, A–G

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.
Diastereoisomer I

1H NMR (300 MHz, CDCl3): δ = 9.77 (t, J = 0.97 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 6.76 (m, 1 H), 6.67 (dd, 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 (dd, J = 1.1, 7.6, 17.6 Hz, 1 H), 2.58–2.47 (m, 1 H), 2.30 (dd, J = 0.9, 5.2, 17.7 Hz, 1 H), 2.11–1.88 (m, 4 H), 1.81–1.71 (m, 1 H).

13C NMR (75 MHz, CDCl3): 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, 34.64, 34.88, 25.67.


Diastereoisomer II

1H NMR (300 MHz, CDCl3): 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 (d, J = 0.3, 1.7, 7.9 Hz, 1 H), 5.92 (s, 2 H), 3.68–3.58 (m, 1 H), 2.99 (dd, J = 1.1, 7.6 Hz, 1 H), 2.30 (dd, J = 0.8, 4.9, 17.6 Hz, 1 H), 2.35–2.17 (m, 2 H), 2.06–1.87 (m, 4 H).

13C NMR (75 MHz, CDCl3): δ = 116.5, 108.6, 108.5, 107.2, 101.0, 41.5, 34.5, 23.1, 22.7.


7-(Benzo[d][1,3]dioxol-5-yl)-4,5,6,7-tetrahydro-1H-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 H2O and EtOAc. The mixture was extracted with EtOAc (3 × 10 mL), dried (Na2SO4), filtered, and concentrated. The crude residue was purified by column chromatography (silica gel, hexane/EtOAc, 15:1). 22 was obtained as a reddish oil; yield: 37 mg (80%).

1H NMR (300 MHz, CDCl3): δ = 7.51 (brs, 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).

13C NMR (75 MHz, CDCl3): δ = 147.9, 146.3, 139.2, 129.0, 121.2, 118.4, 116.5, 108.6, 108.5, 107.2, 101.4, 41.5, 34.5, 23.1, 22.7.


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.). 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.).

Supporting Information

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


