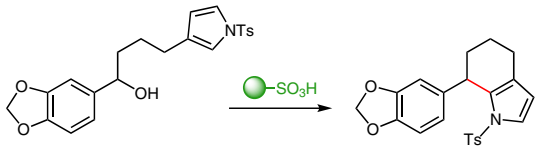
Synthesis B. N. Doan et al. Paper

Synthesis of (±)-γ-Lycorane by Using an Intramolecular Friedel–Crafts Reaction

Bao Nguyen Do Doan
Xin Yi Tan
Chin May Ang
Roderick W. Bates*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, 637371, Singapore
roderick@ntu.edu.sg



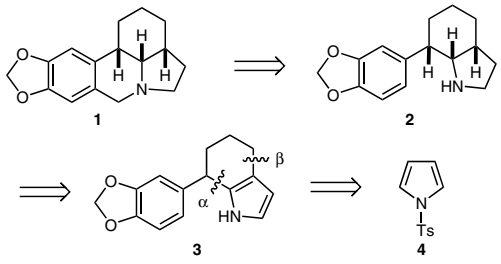
Received: 29.04.2017
Accepted after revision: 26.05.2017
Published online: 20.07.2017
DOI: 10.1055/s-0036-1589067; Art ID: ss-2017-t0284-op

Abstract A total synthesis of γ-lycorane has been achieved by employing *N*-tosylpyrrole as a key building block. The synthesis employs both an intermolecular and an intramolecular Friedel–Crafts reaction, as well as a completely diastereoselective hydrogenation of a late-stage pyrrole intermediate.

Key words heterocycle, pyrrole, Friedel–Crafts, hydrogenation

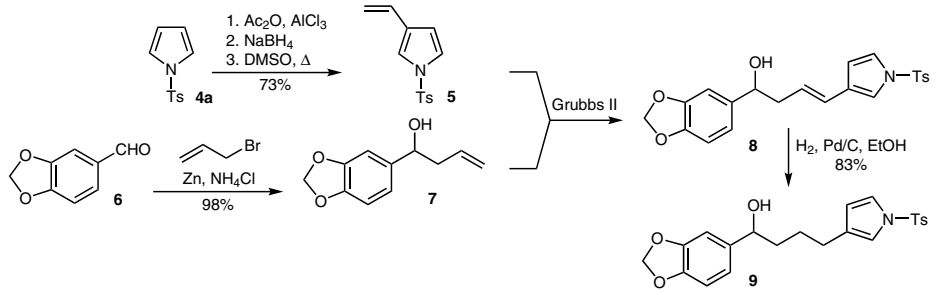
Numerous syntheses of γ-lycorane **1** have been reported despite, as various authors have pointed out, its apparent lack of useful pharmacological properties.[1] Nevertheless, it is one of the prototypical *N*-heterocycles of its group and syntheses of this compound serve to demonstrate the suitability or otherwise of synthetic methodology.

γ-Lycorane **1** may be viewed as a substituted pyrrolidine. One strategy for the synthesis of pyrrolidine natural products is by reduction of the corresponding pyrrole. This strategy has seen some use by organic chemists, but infrequently.[2] An advantage of taking pyrrole as a starting material is that electrophilic substitution can be directed to either the α- or β-positions, depending, principally, on the substitution pattern, especially the identity of the N-substituent.[3] This ability recommends pyrrole as a starting material for γ-lycorane, as both α- and β-substitution are required. It is known that γ-lycorane can be formed by the Pictet–Spengler reaction of pyrrolidine **2**,[1b] which, in turn, might be formed by hydrogenation of pyrrole **3** (Scheme 1). The α- and β-positioned bonds on the pyrrole could then be formed by electrophilic chemistry, with the α-bond put in place by an intramolecular Friedel–Crafts reaction. Indeed, Angle and Boyce have reported such a method.[1s] They used the *N*-TIPS substituent to direct electrophilic substitution to the β-position, then switched to an *N*-Boc group for later chemistry. A disadvantage of using pyrrole is its acid sensitivity. Indeed, Angle and Boyce had to employ an uncommon Lewis acid, $Sn(OTf)_2$, for the second pyrrole bond forming reaction. In contrast, *N*-tosyl pyrrole **4a** is relatively acid stable and the ability of the *N*-tosyl group to direct Friedel–Crafts acylation to the β-position has been well documented.[4] Substitution at the β-position represents the thermodynamic pathway; α-substitution is possible under kinetic control. *N*-Tosyl pyrrole **4a** is also readily available and cheaply prepared.[5]



Scheme 1 γ-Lycorane retrosynthesis

Our plan was to prepare alcohol **8** as the substrate for the α-bond forming intramolecular Friedel–Crafts reaction. In our first approach (Scheme 2), *N*-tosyl pyrrole **4a** was converted into the corresponding 3-vinyl derivative **5** in three steps by the method of Kakushima.[4c] Alcohol **7** was prepared in excellent yield from piperonal **6** by Luche's modification[6] of the Barbier reaction. Cross metathesis between pyrrole **5** and alcohol **7** using the second-generation Grubbs catalyst in toluene gave the desired product **8** in modest yield (Table 1), but exclusively as the *trans* isomer. This is, to our knowledge, the first example of the cross metathesis of a vinyl pyrrole. Much higher yields were obtained when the reaction was carried out in hexafluorobenzene,[7] although higher dilution was helpful. Alkene **8** could be easily hydrogenated, giving alcohol **9** without any complications arising from the presence of the benzylic alcohol.



Scheme 2 The cross-metathesis approach

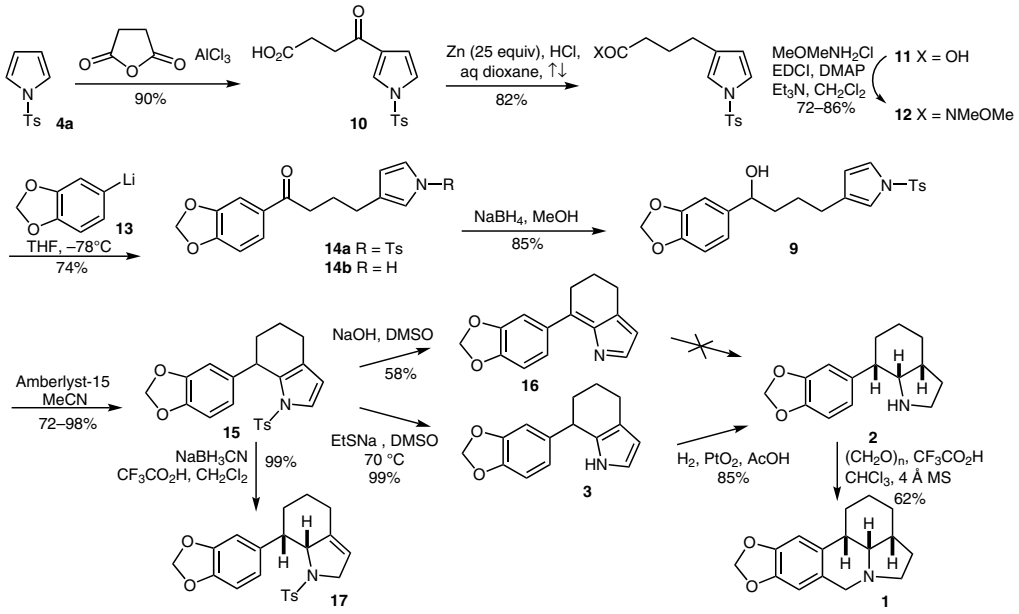
Table 1 Cross-Metathesis Reactions between Alkenes **7** and **5**

Entry	Ratio of **7**/**5**	Solvent	Concn of **5** (M)	*T* (°C)	*t* (h)	Yield (%)
1	1:1	toluene	0.2	70–80	overnight	0
2	1:1	toluene	0.05	70–80	6.5	37
3	3:1	C_6F_6	0.05	reflux	6.5	80
4	3:1	C_6F_6	0.1[a]	reflux	8.5	79
5	3:1	C_6F_6	0.1[b]	reflux	8.5	52
6	3:1	C_6F_6	0.15	reflux	6.5	69

[a] Using 1 mmol of pyrrole **5**.
[b] Using 2 mmol of pyrrole **5**.

Seeking an alternative approach due to the cost of C_6F_6, the need for excess of one metathesis partner, and the difficulties in scale-up, *N*-tosyl pyrrole **4a** was subjected to Friedel–Crafts acylation with succinic anhydride (Scheme 3). The keto group of acid **10** was then deleted by Clemmensen reduction. This reaction sequence dates back to Haworth,[8] who employed zinc amalgam for the reduction. Wishing to avoid the use of mercury for environmental and safety reasons,[9] we found that the same reaction could be accomplished by using a large excess of zinc powder in the presence of HCl, provided that dioxane was employed as the organic co-solvent. The use of toluene was ineffective, while tetrahydrofuran (THF) underwent ring opening under these conditions. When ethanol was used, partial esterification was observed. The resulting acid **11** was then converted into the corresponding Weinreb amide **12**, which was coupled with the lithium derivative **13**.[10] In this transformation, it was found to be essential to maintain the temperature below –50 °C, otherwise partial detosylation of **14a** to the corresponding N-unsubstituted pyrrole **14b** would also be observed. Pyrroles **14a** and **14b** were chromatographically inseparable. Reduction of the ketone with sodium borohydride gave alcohol **9**, which was identical to the material prepared before.

Treatment of alcohol **9** with amberlyst-15 smoothly provided the Friedel–Crafts product **15** in 82% average yield, by formation of the new carbon–carbon bond at the α-position. The reaction proceeded much more rapidly in acetonitrile than in either dichloromethane or chloroform. We also found that scandium triflate[11] was an effective catalyst for this cyclization, but gave a very poor yield (18%). As the *N*-tosyl group had now served its purpose, attempts were made to remove it. With pyrroles, this is typically done by heating with sodium hydroxide.[12] However, no reaction was observed when dioxane or methanol were used as the solvent. We have previously observed that sodium hydroxide is much more reactive in dimethyl sulfoxide (DMSO).[2b] This proved to be so, but, in this case, the result was elimination of tosic acid to give **16**. We attribute this unexpected reactivity to the degree of steric hindrance around the tosyl group of **15**. Reasoning that a stronger nucleophile but a weaker base was required, we employed sodium ethanethiolate and were delighted to find clean detosylation upon heating in DMSO. With the N-unsubstituted pyrrole **3** in hand, we turned to hydrogenation[1b,1s] to convert it into the pyrrolidine. Hydrogenation over Rh/C, Rh/Al_2O_3, or Pd/C proved fruitless,[13] but the method of Kray and Reinecke,[14–16] using platinum oxide in acetic acid and hydrogen under modest pressure, gave pyrrolidine **2** as a single stereoisomer. The presumption that this was the desired isomer was vindicated by the eventual conversion into the natural product. While experimenting with the reduction reaction, we also investigated a modified Knorr–Rabe reduction.[17] Treatment of pyrrole **15** with sodium cyanoborohydride and trifluoroacetic acid gave dihydropyrrole **17** as a ca. 5:1 mixture of stereoisomers. The major isomer was found by X-ray crystallography to possess the desired stereochemistry.[18] As this pathway offered no advantages (and lower ste-



Scheme 3 The second approach and completion of the synthesis

reoselectivity) over the eventual hydrogenation route, it was not continued. The synthesis was completed by treatment of pyrrolidine **2** with paraformaldehyde under acidic conditions in a Pictet–Spengler process to deliver γ-lycorane **1**. The NMR spectroscopic data for our synthetic material were in excellent agreement with those reported previously.[1h]

In conclusion, a diastereoselective synthesis of (±)-γ-lycorane **1** has been completed relying on the robust *N*-tosyl group to control regioselectivity in pyrrole functionalization. Two routes have been developed to access the key Friedel–Crafts precursor: both routes to (±)-γ-lycorane total nine steps.

When appropriate, reactions were run under a nitrogen atmosphere in oven-dried glassware. THF was distilled from sodium/benzophenone, toluene was distilled from sodium, dichloromethane was distilled from calcium hydride, and chloroform was passed through active alumina. Other solvents and reagents were used as received. Column chromatography was carried out on silica gel 230–400 mesh, and analytical TLC on glass plates (silica gel 60, F_{254}). NMR spectra were recorded in $CDCl_3$ solutions at 400 MHz (^{1}H) or 100 MHz (^{13}C). Chemical shifts are given in ppm and coupling constants are given in Hz.

Alcohol 7[19]

Activated zinc (33.4 mmol, 2.18 g, 2 equiv) was added to a solution of piperonal **6** (16.7 mmol, 2.50 g, 1 equiv) in THF (4 mL), followed by saturated NH_4Cl solution (20 mL). The mixture was cooled to 0 °C and distilled allyl bromide (33.4 mmol, 2.90 mL, 2 equiv) was added dropwise. The reaction was stirred overnight. The mixture was then filtered through Celite™ and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. The solution was concentrated to give **7**.

Yield: 3.13 g (98%); orange oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87 (app dd, *J* = 0.4, 1.6 Hz, 1 H), 6.80 (dd, *J* = 1.6, 8.0 Hz, 1 H), 6.77 (dd, *J* = 0.4, 8.0 Hz, 1 H), 5.95 (s, 2 H), 5.85–5.73 (m, 1 H), 5.18–5.11 (m, 2 H), 4.65 (t, *J* = 6.5 Hz), 2.47 (m, 2 H), 2.02 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.7, 146.9, 138.0, 134.4, 119.2, 118.4, 108.0, 106.4, 101.0, 73.2, 43.8.

Alcohol 8

A solution of alcohol **7** (1.50 mmol, 288 mg, 3 equiv) and pyrrole 5 (0.50 mmol, 124 mg, 1 equiv) in C_6F_6 (10 mL) was thoroughly degassed for 15 minutes and then heated at reflux under a continuous nitrogen flow. A solution of Grubbs II catalyst (25 µmol, 23 mg, 5 mol%) in C_6F_6 (5 mL) was added portionwise (1 mL per hour). After adding the last portion, the mixture was further stirred for 2.5 h. The solution was concentrated, and the crude material was purified by flash chromatography, (EtOAc/hexane, gradient 20–40%) to give **8**.

Yield: 164 mg (80%); light-brown oil.

FTIR (KBr): 3416, 3134, 3053, 3147, 2778, 2538, 1919, 1850, 1721, 1654, 1595, 1487, 1367, 1171, 1099, 1061, 1038, 1018, 966, 868, 812, 702, 603 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.0 Hz, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.09–7.02 (m, 2 H), 6.79–6.74 (m, 3 H), 6.37–6.25 (m, 2 H), 5.95–5.84 (m, 1 H), 5.93 (s, 2 H), 4.64 (t, *J* = 6.4 Hz, 1 H), 2.52 (app t, *J* = 6.4 Hz, 2 H), 2.39 (s, 3 H), 2.08 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.7, 146.9, 145.0, 138.0, 135.9, 128.0, 127.3, 126.8, 125.6, 124.7, 121.6, 119.1, 117.8, 111.1, 108.0, 106.3, 101.0, 73.5, 42.9, 21.6.

MS (ESI): *m*/*z* (%) = 412 [M + H]$^+$, 394 (100), 380 (62).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{22}NO_5S$: 412.1219; found: 412.1218.

Alcohol 9 (by Hydrogenation)

Pd/C (15 mg, 10% w/w) was added to a solution of alkene **8** (0.367 mmol, 151 mg) in EtOH (5 mL). The system was then flushed with nitrogen, followed by hydrogen. The mixture was stirred under hydrogen (balloon pressure) for 4 h. The solution was filtered through Celite™ and concentrated to give alcohol **9**.

Yield: 125 mg (83%); pale-yellow solid; mp 90–92 °C.

FTIR (KBr): 3485, 3148, 2725, 2673, 2353, 2309, 2043, 1923, 1857, 1834, 1304, 1250, 1169, 1101, 928, 891, 870, 844, 812, 773, 723, 667, 644 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.0 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 7.05 (dd, *J* = 2.2, 3.2 Hz, 1 H), 6.87–6.85 (m, 1 H), 6.81 (m, 1 H), 6.77–6.72 (m, 2 H), 6.11 (dd, *J* = 1.6, 3.2 Hz, 1 H), 5.95 (s, 2 H), 4.55 (m, 1 H), 2.39 (t, *J* = 6.4 Hz, 2 H), 2.39 (s, 3 H), 1.75 (br. d, *J* = 4 Hz, 1 H), 1.76–1.72 (m, 2 H), 1.65–1.58 (m, 2 H), 1.52–1.44 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 146.9, 144.7, 138.7, 136.3, 129.9, 129.4, 126.7, 120.9, 119.3, 117.3, 114.6, 108.0, 106.3, 101.0, 74.3, 38.4, 26.5, 26.1, 21.6.

MS (ESI): *m*/*z* (%) = 436 $[M + Na]^+$, 396 (100).

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{23}NO_5SNa$: 436.1195; found: 436.1183.

Ketone 10[20]

Succinic anhydride (11.0 mmol, 1.10 g, 1.1 equiv) was added to a suspension of anhydrous $AlCl_3$ (22.0 mmol, 2.93 g, 2.2 equiv) in CH_2Cl_2 (40 mL). The mixture was stirred for 15 minutes until a clear solution was obtained. A solution of *N*-tosyl pyrrole **4** (10.0 mmol, 2.21 g, 1 equiv) in CH_2Cl_2 (5 mL) was added slowly to the mixture, which was stirred at r.t. for 3 h until TLC showed completion. The reaction was quenched with ice water and the organic layer was separated. The remaining aqueous layer was further extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated to give ketone **10**.

Yield: 2.88 g (90%); yellow solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.0 Hz, 2 H), 7.77 (app t, *J* = 2.0 Hz, 1 H) 7.34 (d, *J* = 8.0 Hz, 2 H), 7.14 (dd, *J* = 2.0, 3.2 Hz, 1 H), 6.69–6.67 (dd, *J* = 2.0, 3.2 Hz, 1 H), 3.07 (t, *J* = 6.6 Hz, 2 H), 2.74 (t, *J* = 6.6 Hz, 2 H), 2.42 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.8, 177.8, 146.0, 135.0, 130.4, 128.2, 127.3, 124.3, 121.6, 112.2, 34.0, 27.6, 21.7.

Carboxylic Acid 11[20]

Activated zinc (213 mmol, 13.5 g, 25 equiv), followed by concentrated aqueous hydrochloric acid (5 mL) were added to a refluxing solution of ketone **10** (8.50 mmol, 2.72 g, 1 equiv) in aqueous dioxane (dioxane–water, 9:1, 100 mL). The mixture was maintained at gentle reflux, and concentrated aqueous hydrochloric acid was further added dropwise (1 mL per 10 minutes) until TLC showed completion (ca. 4 h). All excess zinc was quenched with concentrated aqueous hydrochloric acid. The mixture was then diluted with brine and saturated with NaCl. The mixture was extracted with ether (3 × 30 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography ($MeOH/CH_2Cl_2$, 3%) to give acid **11**.

Yield: 2.14 g (82%); colorless solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.0 Hz, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.07 (dd, *J* = 2.4, 3.2 Hz, 1 H), 6.91 (dd, *J* = 1.6, 2.4 Hz, 1 H), 6.14 (dd, *J* = 1.6, 3.2 Hz, 1 H), 2.44 (t, *J* = 7.5 Hz, 2 H), 2.39 (s, 3 H), 2.32 (t, *J* = 7.5 Hz, 2 H), 1.84 (quint, *J* = 7.5 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.7, 144.8, 136.1, 129.9, 128.3, 126.7, 121.1, 117.5, 114.4, 33.2, 25.9, 24.8, 21.5.

Amide 12

Triethylamine (15.0 mmol, 2.10 mL, 2 equiv) was added dropwise to a solution of acid **11** (7.47 mmol, 2.30 g, 1 equiv) and *N*,*O*-dimethylhydroxylamine hydrochloride (11.2 mmol, 1.09 g, 1.5 equiv) in anhydrous CH_2Cl_2 (40 mL) at 0 °C. EDCI·HCl (11.2 mmol, 2.15 g, 1.5 equiv) and DMAP (1.49 mmol, 183 mg, 0.2 equiv) were added as solids to the solution, and the mixture was allowed to warm to r.t. The mixture was stirred overnight, then the solution was washed with 2 M aq. HCl (2 × 30 mL), saturated $NaHCO_3$ solution (30 mL) and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (EtOAc/hexane, 40–50%) to give amide **12**.

Yield: 2.24 g (86%); pale-yellow oil.

FTIR (KBr): 3134, 2927, 2870, 2822, 2587, 2532, 1921, 1790, 1732, 1634, 1595, 1360, 1308, 1292, 1258, 1173, 1101, 1061, 995, 957, 916, 870, 814, 779, 704 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.0 Hz, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.07 (dd, *J* = 2.4, 3.2 Hz, 1 H), 6.91 (dd, *J* = 1.6, 2.4, 1 H), 6.15 (dd, *J* = 1.6, 3.2 Hz, 1 H), 3.61 (s, 3 H), 3.16 (s, 3 H), 2.44 (t, *J* = 7.0 Hz, 2 H), 2.39 (s, 3 H), 2.39 (t, *J* = 7.0 Hz, 2 H), 1.85 (quint, *J* = 7.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 144.7, 136.2, 129.9, 129.0, 126.7, 120.9, 117.4, 114.5, 61.1, 32.1, 31.1, 26.2, 24.7, 21.6.

MS (ESI): *m*/*z* (%) = 351 $[M + H]^+$, 290 (9).

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{23}N_2O_4S$: 351.1379; found: 351.1377.

Ketone 14a

n-BuLi (1.6 M in hexane, 5.6 mL, 2.2 equiv) was added slowly to a solution of 5-bromo-1,3-benzodioxole (7.29 mmol, 1.47 g, 1.80 equiv) in anhydrous THF (60 mL) at −78 °C. The resulting solution was stirred at −78 °C for 1 h. A solution of amide **12** (4.05 mmol, 1.42 g, 1 equiv) in anhydrous THF (15 mL) was added dropwise while the temperature was maintained between −78 °C and −55 °C. After addition, the mixture was stirred at −78 °C for 1 h, until TLC showed completion. The reaction was quenched at −78 °C with saturated $NaHCO_3$ solution (50 mL), and the mixture was allowed to warm to r.t. The mixture was then extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated. The residue was purified by flash chromatography (EtOAc/hexane, gradient 10–20%) to give **14a**.

Yield: 1.23 g (74%); pale-purple solid; mp 93–96 °C.

FTIR (KBr): 2723, 2669, 2357, 2340, 1667, 1304, 1242, 1169, 1103, 1034, 928, 891, 768, 721 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.0 Hz, 2 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.38 (app s, 1 H), 7.27 (d, *J* = 8 Hz, 2 H), 7.08 (t, *J* = 2.4 Hz, 1 H), 6.91 (m, 1 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 6.16 (m, 1 H), 6.04 (s, 2 H), 2.84 (t, *J* = 7.0 Hz, 2 H), 2.47 (t, *J* = 7.0 Hz, 2 H), 2.38 (s, 3 H), 1.94 (quint, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.1, 151.6, 148.1, 144.7, 136.2, 131.8, 129.9, 128.9, 126.7, 124.1, 121.1, 117.5, 114.5, 107.8, 101.8, 37.4, 26.2, 24.6, 21.6.

MS (ESI): *m*/*z* = 412 $[M + H]^+$.

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{22}NO_5S$: 412.1219; found: 412.1214.

Alcohol 9 (by Ketone Reduction)

$NaBH_4$ (9.39 mmol, 355 mg, 3 equiv) was added portionwise to a solution of ketone **12** (3.13 mmol, 1.29 g, 1 equiv) in MeOH (60 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min until TLC showed completion. The mixture was diluted cautiously with water (50 mL). All of the volatiles were then removed, and the remaining aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (EtOAc/hexane, 30%) to give alcohol **9**.

Yield: 1.11 g (85%); colorless crystalline solid; identical to the material prepared earlier.

Pyrrole 15

Amberlyst-15 (222 mg, 20% w/w) was added to a solution of alcohol **9** (2.68 mmol, 1.11 g, 1 equiv) in acetonitrile (60 mL). The solution was stirred at r.t. for 2 h until TLC showed completion. The solution was filtered and concentrated to give pyrrole **15**, which was used directly in the next reaction without further purification.

Yield: 1.04 g (98%); colorless solid; mp 181–183 °C.

FTIR (KBr): 3169, 2723, 2669, 2407, 1902, 1850, 1736, 1634, 1597, 1313, 1288, 1238, 1169, 1122, 1094, 1059, 1040, 993, 937, 926, 902, 858, 808, 781, 721, 671 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 3.4 Hz, 1 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 6.99 (d, *J* = 8.0 Hz, 2 H), 6.49 (d, *J* = 8.0 Hz, 1 H), 6.30 (dd, *J* = 1.6, 8 Hz, 1 H), 6.15 (d, *J* = 3.4 Hz, 1 H), 6.13 (d, *J* = 1.6 Hz, 1 H), 5.84 (m, 2 H), 4.50–4.49 (m, 1 H), 2.57–2.42 (m, 2 H), 2.33 (s, 3 H), 2.03–1.94 (m, 1 H), 1.76–1.72 (m, 1 H), 1.55–1.50 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.9, 145.5, 143.6, 138.7, 135.9, 129.9, 129.1, 126.7, 124.9, 121.9, 121.4, 111.6, 108.8, 107.7, 100.6, 37.8, 32.7, 22.9, 21.5, 16.7.

MS (ESI) *m*/*z* = 396 $[M + H]^+$.

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{22}NO_4S$: 396.1270; found: 396.1262.

Alkylidene Pyrrole 16

Solid sodium hydroxide (6.06 mmol, 242 mg, 20 equiv) was added to a solution of pyrrole **15** (0.303 mmol, 120 mg, 1 equiv) in DMSO (5 mL). The mixture was stirred at r.t. overnight until TLC showed completion. The solution was diluted with water (50 mL) and the mixture was then extracted with Et_2O (6 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (EtOAc/hexane, 40%) to give **16**.

Yield: 43 mg (58%); pale-yellow solid; mp 185–187 °C.

FTIR (KBr): 3167, 2723, 2669, 2407, 1921, 1651, 1304, 1284, 1248, 1227, 1153, 1101, 1036, 961, 928, 903, 874, 814, 723 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 (br s, 1 H), 6.89–6.83 (m, 3 H), 6.00 (s, 2 H), 5.80 (app s, 1 H), 2.68 (app t, *J* = 7.0 Hz, 2 H), 2.60 (t, *J* = 7.0 Hz, 2 H), 1.96 (quint, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 149.5, 148.3, 147.6, 133.7, 132.2, 123.2, 121.4, 115.6, 108.7, 107.6, 101.4, 29.3, 24.2, 23.6.

MS (ESI): *m*/*z* (%) = 256 (100) $[M + OH]^+$.

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{14}NO_2$: 240.1025; found: 240.1020.

Pyrrole 3

Pyrrole **15** (138 mg, 1 equiv, 0.349 mmol) was added to a solution of EtSH (4 mL) and NaOH (5.24 mmol, 210 mg, 15 equiv) in DMSO (20 mL). The solution was then warmed to 60–70 °C and stirred under nitrogen overnight. After TLC showed completion, the solution was allowed to cool to r.t. and diluted with water (200 mL). The mixture was extracted with Et_2O (8 × 15 mL) and the combined organic layers were shaken vigorously with 5% aqueous H_2O_2 (20 mL) for 10 seconds. The aqueous layer was separated; the remaining organic layer was washed with saturated Na_2SO_3 solution (20 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (EtOAc/hexane, 5%) to give pyrrole **3**.

Yield: 83 mg (99%); pink oil.

FTIR (KBr): 3418, 2928, 2851, 2778, 2683, 2538, 2307, 2041, 1919, 1850, 1674, 1607, 1504, 1485, 1435, 1368, 1186, 1117, 1038, 931, 858, 812 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.50 (br s, 1 H), 6.73 (app dd, *J* = 1.0, 7.0 Hz, 1 H), 6.64–6.59 (m, 3 H), 6.01 (app t, *J* = 2.4 Hz, 1 H), 5.92 (m, 2 H), 3.91 (app t, *J* = 6 Hz, 1 H), 2.62–2.59 (m, 2 H), 2.16–2.10 (m, 1 H), 1.90–1.87 (m, 1 H), 1.76–1.67 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 146.1, 139.1, 128.8, 121.1, 118.2, 116.4, 108.4, 108.1, 107.1, 100.9, 40.9, 34.3, 23.0, 22.6.

MS (ESI) *m*/*z* = 242 $[M + H]^+$.

HRMS (ESI-TOF): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{16}NO_2$: 242.1181; found: 242.1179.

Pyrrolidine 2[1h]

PtO_2 (11 mg, 30% w/w) was added to a solution of pyrrole **3** (0.133 mmol, 32 mg, 1 equiv) in glacial acetic acid (3 mL) in a Fisher–Porter tube. The solution was then placed under H_2 atmosphere (100 psi) and stirred overnight. The reaction was quenched with 2 M NaOH solution (20 mL), and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (10% MeOH/1% Et_3N/$CHCl_3$) to give pyrrolidine **2**.

Yield: 28 mg (85%); yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.78 (s, 1 H), 6.76–6.72 (m, 2 H), 5.91 (s, 2 H), 3.19–3.17 (m, 1 H), 3.07–2.98 (m, 1 H), 2.85–2.76 (m, 1 H), 2.07–1.21 (m, 9 H).

γ-Lycorane 1[1h]

Paraformaldehyde (0.675 mmol, 21 mg, 5 equiv) was added to a solution of pyrrolidine **2** (0.135 mmol, 33 mg, 1 equiv) in anhydrous $CHCl_3$ (5 mL). The mixture was stirred at r.t. for 5 min. Trifluoroacetic acid (2.70 mmol, 210 µL, 20 equiv), followed by 4Å molecular sieves (300 mg), were added. The solution was heated at gentle reflux overnight. The reaction was quenched by addition of 2 M NaOH (10 mL). The organic layer was collected, and the remaining aqueous layer was further extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (MeOH/$CHCl_3$, 5%) to give γ-lycorane **1**.

Yield: 21 mg (62%); yellow solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.62 (s, 1 H), 6.50 (s, 1 H), 5.90–5.88 (m, 2 H), 4.03 (d, *J* = 14.0 Hz, 1 H), 3.45–3.33 (m, 1 H), 3.23 (d, *J* = 14.0 Hz, 1 H), 2.82–2.70 (m, 1 H), 2.46–2.33 (m, 1 H), 2.27–2.10 (m, 2 H), 2.07–1.98 (m, 1 H), 1.80–1.25 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 145.1, 133.2, 127.4, 108.3, 106.2, 100.7, 63.0, 57.1, 53.7, 39.4, 37.3, 31.7, 30.4, 29.3, 25.2.

Dihydropyrrole 17

Trifluoroacetic acid (2 mL) was added to a solution of **15** (0.126 mmol, 50 mg, 1 equiv) in CH_2Cl_2 (4 mL). The mixture was cooled to 0 °C in an ice bath and $NaBH_3CN$ (0.378 mmol, 24 mg, 3 equiv) was added in one portion. The reaction was then warmed to r.t. and stirred for 1 h until TLC showed completion. Saturated Na_2CO_3 solution (15 mL) was added to quench the reaction, then the organic layer was separated and the remaining aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (EtOAc/hexane, 10%) to give dihydropyrrole **17**. A crystal that was suitable for X-ray analysis was grown from a $CHCl_3$/hexane mixture.

Yield: 49 mg (99%); reddish solid; d.r. ca. 5:1 (inseparable).

^{1}H NMR (major isomer, 400 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 8.2 Hz, 2 H), 7.19 (d, *J* = 8.2 Hz, 2 H), 6.79–6.69 (m, 3 H), 5.90 (s, 2 H), 4.53 (m, 1 H), 4.10–4.07 (m, 1 H), 3.89–3.88 (m, 1 H), 3.62–3.61 (m, 1 H), 2.61–2.57 (m, 1 H), 2.38 (s, 3 H), 2.08–2.04 (m, 2 H), 1.91–1.81 (m, 2 H), 1.69–1.50 (m, 2 H).

Funding Information

We thank the Agency for Science Technology and Research (A-Star) for financial support of this work (PSF grant number 1321202095). B.N.D.D. thanks the URECA programme of NTU for support.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589067.

References

(1) For selected syntheses, see: (a) Liu, D.; Ai, L.; Li, F.; Zhao, A.; Chen, J.; Zhang, H.; Liu, J. *Org. Biomol. Chem.* **2014**, *12*, 3191. (b) Huntley, R. J.; Funk, R. J. *Tetrahedron Lett.* **2011**, *52*, 6671. (c) Tomooka, K.; Suzuki, M.; Uehara, K.; Shimada, M.; Akiyama, T. *Synlett* **2008**, 2518. (d) El Bialy, S. A. A. *Nat. Prod. Res.* **2008**, *22*, 1176. (e) Chapsal, B. D.; Ojima, I. *Org. Lett.* **2006**, *8*, 1395. (f) Fujioka, H.; Murai, K.; Ohba, Y.; Hirose, H.; Kita, Y. *Chem. Commun.* **2006**, 832. (g) Dong, L.; Xu, Y.-J.; Cun, L.-F.; Cui, X.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2005**, *7*, 4285. (h) Gao, S.; Tu, Y. Q.; Song, Z.; Wang, A.; Fan, X.; Jiang, Y. *J. Org. Chem.* **2005**, *70*, 6523. (i) Yasuhara, T.; Osafune, E.; Nishimura, K.; Yamashita, M.; Yamada, K.-i.; Muraoka, O.; Tomioka, K. *Tetrahedron Lett.* **2004**, *45*, 3043. (j) Shao, Z.; Chen, J.; Huang, R.; Wang, C.; Li, H.; Zhang, H. *Synlett* **2003**, 2228. (k) Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2001**, *66*, 1716. (l) Banwell, M. G.; Harvey, J. E.; Hockless, D. C. R. *J. Org. Chem.* **2000**, *65*, 4241. (m) Hoang-Cong, X.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2125. (n) Cassayre, J.; Zard, S. Z. *Synlett* **1999**, 501. (o) Cossy, J.; Tresnard, L.; Pardo, D. G. *Eur. J. Org. Chem.* **1999**, 1925. (p) Cossy, J.; Tresnard, L.; Pardo, D. G. *Tetrahedron Lett.* **1999**, *40*, 1125. (q) Ikeda, M.; Ohtani, S.; Sato, T.; Ishibashi, H. *Synthesis* **1998**, 1803. (r) Yoshizaki, H.; Satoh, H.; Sato, Y.; Nukui, S.; Shibasaki, M.; Mori, M. *J. Org. Chem.* **1995**, *60*, 2016. (s) Angle, S. R.; Boyce, J. P. *Tetrahedron Lett.* **1995**, *36*, 6185. (t) Banwell, M. G.; Wu, A. W. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2671. (u) Grotjahn, D. B.; Vollhardt, K. P. C. *Synthesis* **1993**, 579. (v) For a review of the synthesis of amaryllidaceae alkaloids, see: Ghave, M.; Froese, J.; Pour, M.; Hudlicky, T. *Angew. Chem. Int. Ed.* **2016**, *55*, 5642.

(2) For a review, see: (a) Jefford, C. W. *Curr. Org. Chem.* **2000**, *4*, 205. (b) For an example from this laboratory, see: Bates, R. W.; Sridhar, S. *J. Org. Chem.* **2011**, *76*, 5026.

(3) For a review of achieving β-substitution in pyrroles, see: Anderson, H. J.; Loader, C. E. *Synthesis* **1985**, 353.

(4) (a) Xu, R. X.; Anderson, H. J.; Gogan, N. J.; Loader, C. E.; McDonald, R. *Tetrahedron Lett.* **1981**, *22*, 4899. (b) Rokach, J.; Hamel, P.; Kakushima, M. *Tetrahedron Lett.* **1981**, *22*, 4901. (c) Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214. (d) Settambolo, R.; Lazzaroni, R.; Messeri, T.; Mazzetti, M.; Salvadori, P. *J. Org. Chem.* **1993**, *58*, 7889.

(5) From 2,5-dimethoxytetrahydrofuran by the Clausson-Kaas method: Elming, N.; Clausson-Kaas, N. *Acta Chem. Scand.* **1952**, *6*, 867.

(6) Pétrier, C.; Luche, J.-L. *J. Org. Chem.* **1985**, *50*, 910.

(7) Samojłowitz, C.; Niebiek, M.; Pazio, A.; Makal, A.; Woźniak, K.; Poater, A.; Cavallo, L.; Wójcik, J.; Zdanowski, K.; Grela, K. *Chem. Eur. J.* **2011**, *17*, 12981.

(8) Haworth, R. D. *J. Chem. Soc.* **1932**, 1125.

(9) (a) *Practical Synthetic Organic Chemistry*; Caron, S., Ed.; J. Wiley & Sons: New York, **2009**. (b) Yamamura, S.; Toda, M.; Hirata, Y. *Org. Synth.* **1973**, *53*, 86. (c) Yamamura, S.; Toda, M.; Hirata, Y. *Chem. Commun.* **1968**, 1494.

(10) Hamze, A.; Giraud, A.; Messaoudi, S.; Provot, O.; Peyrat, J.-F.; Bignon, J.; Liu, J.-M.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami, M. *ChemMedChem* **2009**, *4*, 1912.

(11) Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15.

(12) Jolicoeur, B.; Chapman, E. E.; Thompson, A.; Lubell, W. D. *Tetrahedron* **2006**, *62*, 11531.

(13) For the catalytic hydrogenation of pyrroles, see: *Hydrogenation Methods*; Rylander, P. N., Ed.; Academic Press: London, **1985**, 134.

(14) Kray, L. R.; Reinecke, M. G. *J. Org. Chem.* **1967**, *32*, 225.

(15) It is essential that all traces of thiol from the detosylation step are removed prior to hydrogenation.

(16) To our surprise, attempted hydrogenation of elimination product **16** under the same conditions yielded only a complex mixture.

(17) You, H. T.; Grosse, A. C.; Howard, J. K.; Hyland, C. J. T.; Just, J.; Molesworth, P. P.; Smith, J. A. *Org. Biomol. Chem.* **2011**, *9*, 3948.

(18) CCDC 1534656 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(19) Riflade, B.; Lachkar, D.; Oble, J.; Li, J.; Thorimbert, S.; Hasenkopf, B.; Lacote, E. *Org. Lett.* **2014**, *16*, 3860.

(20) Wu, Z.; Li, Y.; Cai, Y.; Yuan, J.; Yuan, C. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4903.