Tetrahedron Letters 52 (2011) 6671–6674

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Total synthesis of (±)-γ-lycorane via the electrocyclic ring closure of a divinylpyrroline

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ARTICLE INFO

Article history:
Received 7 September 2011
Revised 24 September 2011
Accepted 29 September 2011
Available online 14 October 2011

Keywords:
Amaryllidaceae alkaloids
Indolizidine
Electrocyclic ring closure
Divinylpyrroline

ABSTRACT

A concise total synthesis of (±)-γ-lycorane is described. The key step in the synthesis is the 6π-electrocyclic ring closure of a divinylpyrroline to give a tetrahydroindole, which is subsequently hydrogenated to give the all-*cis* indolizidine core.

The *Amaryllidaceae* family of natural products[1] encompasses a structurally diverse range of compounds with a host of biological activities, and has seen extensive investigation by synthetic chemists. In particular, the lycorane sub-class[2] has for decades served as a test-ground for a range of synthetic methodologies. In fact, since its initial synthesis in 1966 one single member of this family, γ-lycorane (**1**, Fig. 1), has been prepared in both racemic[3] and enantioenriched[4] form by over twenty different research groups using a multitude of synthetic approaches.

These approaches can broadly be grouped according to the order in which the remaining two rings are constructed from an initial bicyclic compound. All of the approaches to date conclude with construction of the B ring, often by Pictet–Spengler or Bischler–Napierelski cyclization. This allows the existing syntheses to be classed into three groups, based on the order or ring construction.

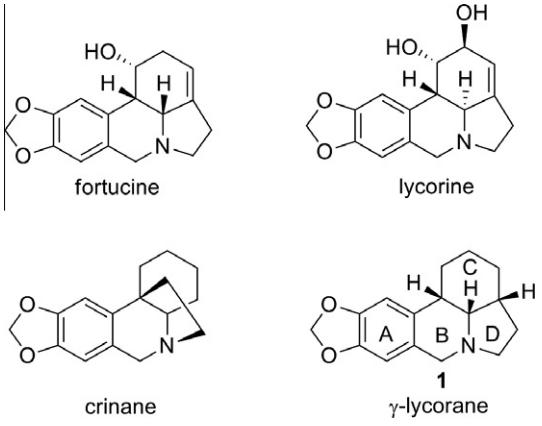

Figure 1. Selected *Amaryllidaceae* alkaloids.

CD → CDA → CDAB approaches

Two examples of the CD→CDA→CDAB approach are shown in Scheme 1. In the first example,[3c] an intramolecular furan-acrylate cycloaddition is performed on amidofuran **2** to form the CD ring system **3**. The A ring is subsequently introduced by acylation, to give aryl amide **4**, which is subsequently transformed into the natural product (±)-**1**.

In the second example,[4b] Fujioka and Kita prepare the CD ring system by means of an intramolecular haloamination reaction. Condensation of aldehyde **5** with amine **6** gave an aminal that was directly treated with NBS to give bromoaminal **7**. A subsequent four step sequence revealed a bromoindolizidinone, to which the piperonyl A ring was appended. A subsequent intramolecular Friedel–Crafts reaction and reduction of the resultant amide gave (−)-γ-lycorane (**1**).

AC → ACD → ACDB approaches

Gong and co-workers' concise synthesis[4c] began with preparation of an AC ring congener by means of an asymmetric nitroallylation reaction. Treatment of allylic acetate **9** with 3,4-(methyl

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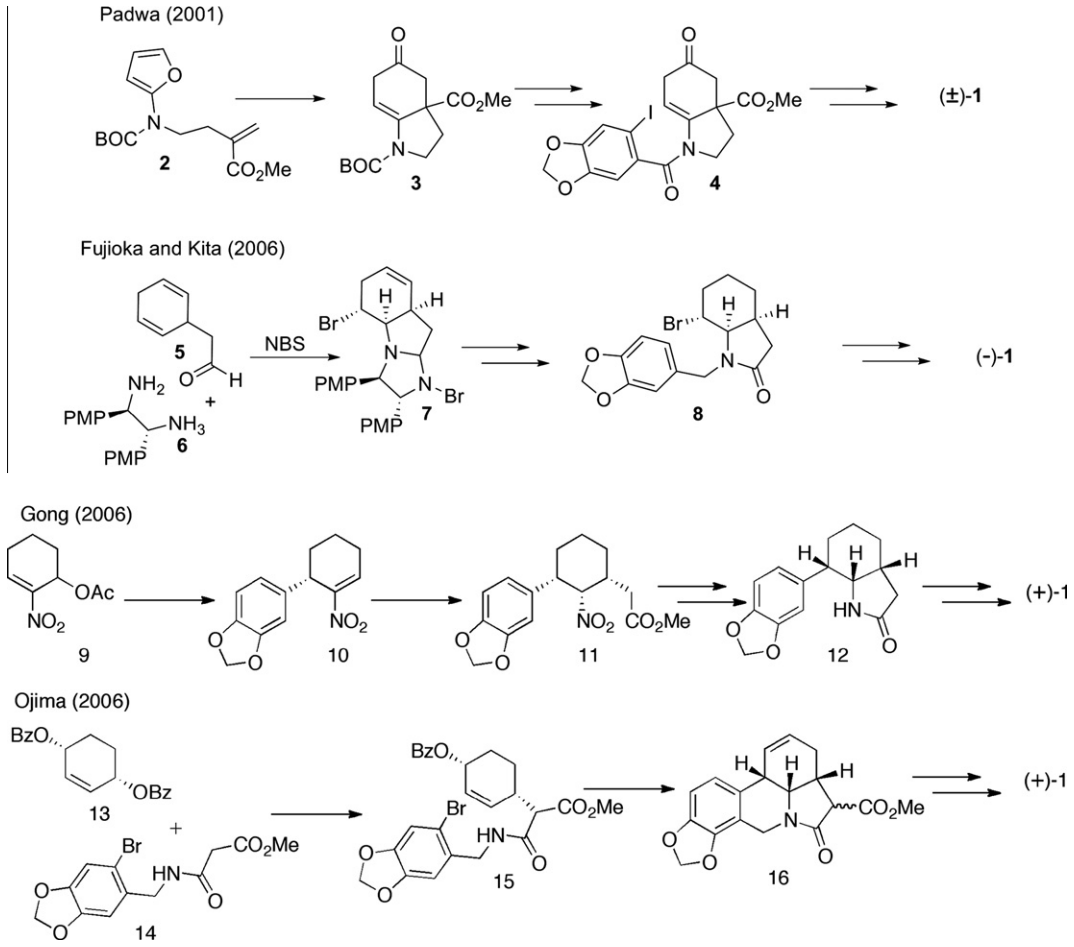
doi:10.1016/j.tetlet.2011.09.138



Scheme 1. CD→CDA→CDAB and AC→ACD→ACDB approaches to γ-lycorane (**1**).

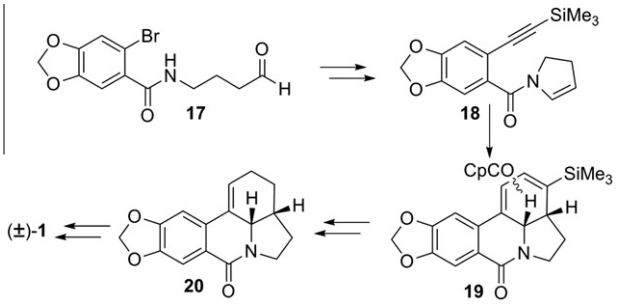
enedioxy)phenylboronic acid in the presence of a rhodium/BINAP catalyst effected allylation to give aryl cyclohexene **10**. Conjugate addition of methyl acetate enolate followed by reduction of the nitro substituent with concomitant lactamization gave indolizidinone **12**, which was subsequently converted to (+)-γ-lycorane (**1**).

In a second example of an AC→ACD→ACDB approach, Ojima and Chapsal have reported a recent synthesis,[4a] drawing heavily on earlier work by Mori,[4f] in which the A and C rings of γ-lycorane are coupled by means of an allylic alkylation reaction. Dibenzoate **13** was treated with the malonate half-amide **14** in the presence of a monodentate phosphoramidite palladium complex to give the desymmetrized benzoate **15**. A subsequent palladium catalyzed tandem allylic amination-intramolecular Heck reaction gave the completed ring system **16**.

AD → ADC → ADCB approaches

The final class of approaches, beginning with the construction of an AD ring congener, has seen little use, with only two reported syntheses. In the first synthesis by the Vollhardt laboratory,[3i] aldehyde **17** is elaborated to acyl pyrroline **18** (Scheme 2). Treatment with $CpCo(CO)_2$ and irradiation effected closure of the C and B rings to give cyclization product **19**. Subsequent demetalation and reduction steps gave (±)-γ-lycorane (**1**).

The second example of this strategy, reported by Angle and Boyce,[3h] begins with Weinreb amide **21**, available in six steps from TIPS-pyrrole. Addition of piperonyllithium to this amide and reduction of the resultant ketone gave benzylic alcohol **23** (Scheme 3). Upon

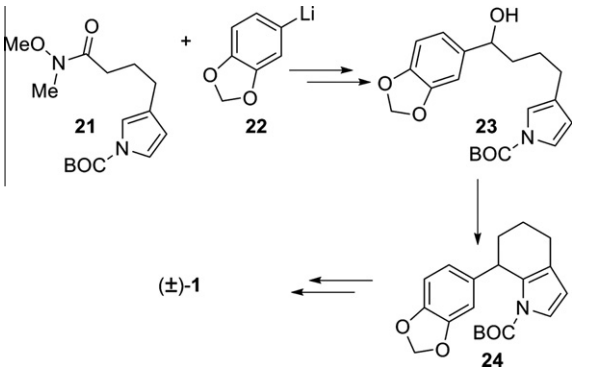


Scheme 2. Vollhardt AD→ADC→ADCB approach to γ-lycorane (**1**).

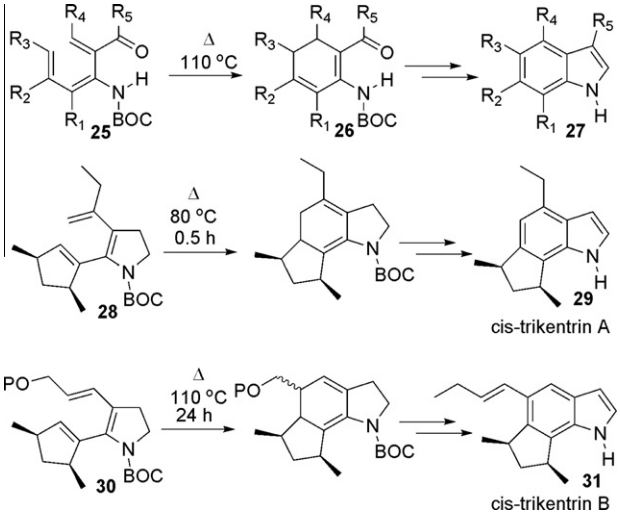
treatment with $Sn(OTf)_2$ the alcohol undergoes a cationic cyclization, forming the C ring. Subsequent hydrogenation and closure of the B ring gave (±)-γ-lycorane (**1**).

We felt that we could prepare γ-lycorane via the less common AD→ADC→ADBC approach using a modification of methodology recently developed in our laboratory for the synthesis of indoles. This methodology makes use of electrocyclic ring closures of trienecarbamates **25** for the synthesis of highly substituted indole ring systems (Scheme 4).[5]

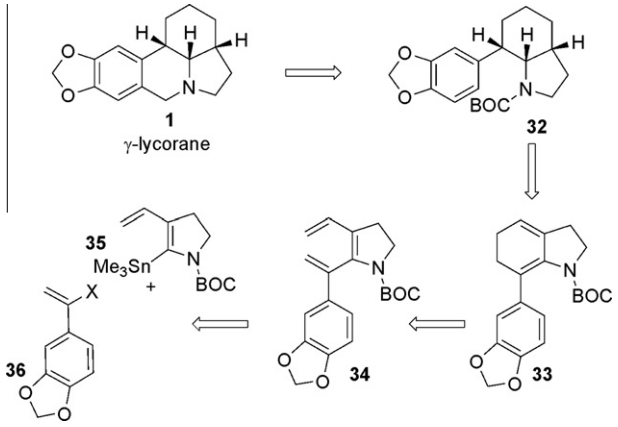
The utility of this methodology for the synthesis of natural products has been demonstrated, first through synthesis of the welwistatin A ring system,[6] and subsequently via syntheses of (±)-*cis*-trikentrin A (**29**) and B (**31**)[7] from divinylpyrroline substrates **28** and **30**. In each case, the dihydroaniline intermediates generated



Scheme 3. Angle AD→ADC→ADCB approach to γ-lycorane (**1**).



Scheme 4. Indole syntheses via trienecarbamate electrocyclizations.

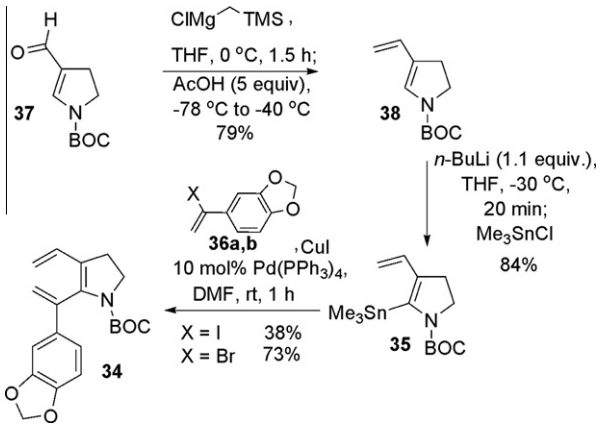


Scheme 5. Retrosynthetic analysis for the synthesis of γ-lycorane (**1**).

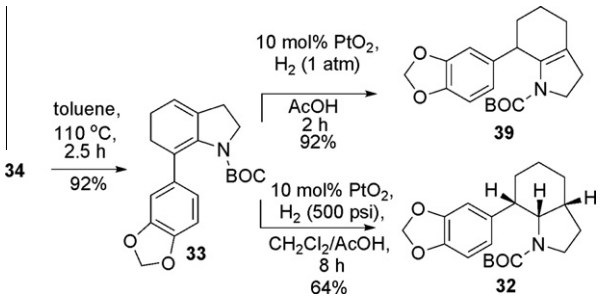
from the electrocyclic closures are oxidized to give, ultimately, indole ring systems.

While all of the examples we have reported to date involve aromatization of the dihydroaniline cyclization products, we felt this methodology could be extended to nonaromatic carbocyclic ring systems as well. In particular, γ-lycorane seemed to offer us an ideal initial substrate upon which we could test our methodology.

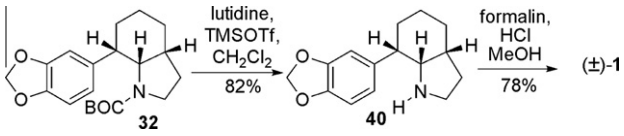
Our retrosynthetic analysis for the synthesis of γ-lycorane (**1**) is shown in Scheme 5. We envisaged that the natural product would



Scheme 6. Preparation of trienecarbamate **34**.



Scheme 7. Preparation of the indolizidine substructure of γ-lycorane (**1**).



Scheme 8. Completion of the γ-lycorane (**1**) total synthesis.

be formed from indolizidine **32**. This amine, in turn, could be derived by asymmetric hydrogenation of diene **33**. This diene would result from the 6π-electrocyclic ring closure of divinylpyrroline **34**, which would in turn be derived from stannane **35** via Stille coupling with the appropriate vinyl halide **36**.

To that end, stannane **35** was prepared by Peterson olefination of aldehyde **37** followed by stannylation at C(2) with *n*-BuLi/trimethyltinchloride[5] (Scheme 6). Initial attempts at Stille coupling with the moderately unstable vinyl iodide **36a**[8] gave poor yields of the desired triene **34**.

The more stable bromide **36b**[9] gave the desired triene in acceptable yield however.

With our key substrate in hand, we were pleased to discover that the 6π-electrocyclic ring closure proceeded smoothly in refluxing toluene to give tetrahydroindole **33** in excellent yield (Scheme 7).

Our attention then turned to the hydrogenation of this diene. Under simple heterogeneous palladium catalyzed hydrogenation conditions enecarbamate **39** was formed. While this adduct could be reduced to the desired indolizidine core of γ-lycorane diastereoselectively under more forceful conditions, it was ultimately determined to be more expedient to reduce both double bonds in a single pot using PtO_2 in acetic acid, giving indolizidine **32** directly.

With this racemic material in hand we then examined conditions for the corresponding asymmetric hydrogenation of diene

33. Catalytic asymmetric hydrogenation of enamides has been extensively studied, however, there remains limited precedent for the reduction of tetrasubstituted systems. We therefore entered this investigation with some trepidation.

We began with a brief screening of three Rh-ligand systems, DuPhos,[10] TangPhos,[11] and BINAP.[12] ^{1}H NMR analysis of the crude mixtures revealed that in each of these cases 1,4-hydrogenation to enecarbamate **39** was predominating. Unfortunately, chiral HPLC analysis of the products revealed negligible enantioselectivity.

Use of a monodentate phosphoramide catalyst[13] also proved unrewarding, failing to give any identifiable hydrogenation products. Discouraged by the lack of even modest selectivity in this initial screening, we quickly turned our efforts to the synthesis of racemic material.

To that end, deprotection[14] of the carbamate was undertaken to give **40** (Scheme 8), whose spectra correlated well with previously published material.[3j] Pictet–Spengler ring closure under the conditions reported by Umezawa[3n] gave γ-lycorane (**1**).

In conclusion, we have completed a concise total synthesis of γ-lycorane in 9 steps from commercially available BOC-2-pyrrolidinone, demonstrating the utility of electrocyclic ring closures of divinylpyrrolines for the synthesis of indolizidine ring systems. Application of this methodology in the synthesis of other ring systems embodied in biologically active natural products is underway in our laboratories.

Acknowledgment

We appreciate the financial support provided by the National Institutes of Health (GM28663).

References and notes

1. Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, pp 251–376.
2. Lewis, J. R. *Nat. Prod. Rep.* **1994**, *11*, 329.
3. (a) Gao, S.; Tu, Y. Q.; Song, Z.; Wang, A.; Fan, X.; Jiang, Y. *J. Org. Chem.* **2005**, 6523; (b) Yasuhara, T.; Osafune, E.; Nishimura, K.; Yamashita, M.; Yamada, K.-I.; Muraoka, O.; Tomioka, K. *Tetrahedron Lett.* **2004**, *45*, 3043; (c) Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2001**, *66*, 1716; (d) Shao, Z.; Chen, J.; Huang, R.; Wang, C.; Li, L.; Zhang, H. *Synlett* **2003**, 2228; (e) Cassayre, J.; Zard, S. Z. *Synlett* **1999**, 504; (f) Hoang-Cong, Z.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2125; (g) Cossy, J.; Tresnard, L.; Pardo, D. G. *Eur. J. Org. Chem* **1999**, 1925; (h) Angle, S. R.; Boyce, J. P. *Tetrahedron Lett.* **1995**, *36*, 6185; (i) Grotjahn, D. B.; Vollhardt, P. C. *Synthesis* **1993**, 579; (j) Pearson, W. H.; Schkeryantz, J. M. *J. Org. Chem.* **1992**, *57*, 6783; (k) Baeckvall, J. E.; Anderson, P. G.; Stone, G. B.; Gogoll, A. *J. Org. Chem.* **1991**, *56*, 2988; (l) Hwang, H.; Magnus, P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 693; (m) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1979**, *44*, 1074; (n) Umezawa, B.; Hoshino, O.; Sawaki, S.; Sato, S.; Numao, N. *J. Org. Chem.* **1977**, *42*, 4272; (o) Iida, H.; Aoyagi, S.; Kibayashi, C. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2502; (p) Hara, H.; Hoshino, O.; Umezawa, B. *Tetrahedron Lett.* **1972**, *13*, 5031; (q) Ganem, B. *Tetrahedron Lett.* **1971**, *12*, 105; (r) Irie, H.; Nishutani, Y.; Sugita, M.; Uyeo, S. *J. Chem. Soc., Chem. Commun.* **1970**, 1313; (s) Ueda, N.; Tokuyam, T.; Sakan, T. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2012.
4. (a) Chapsal, B. D.; Ojima, I. *Org. Lett.* **2006**, *8*, 1395; (b) Fujioka, H.; Murai, K.; Ohba, Y.; Hirose, H.; Kita, Y. *Chem. Commun.* **2006**, 832; (c) Dong, L.; Xu, Y.-J.; Cun, L.-F.; Cui, X.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2005**, *7*, 4285; (d) Banwell, M. G.; Harvey, J. E.; Hockless, D. C. R. *J. Org. Chem.* **2000**, *65*, 4241; (e) Ikeda, M.; Ohtani, S.; Sato, T.; Ishibashi, H. *Synthesis* **1998**, 1803; (f) Yoshizki, H.; Satoh, H.; Sato, S.; Nukui, S.; Shibasaki, M.; Mori, M. *J. Org. Chem.* **1995**, *60*, 2016.
5. Greshock, T. J.; Funk, R. L. *J. Am. Chem. Soc.* **2006**, *128*, 4946.
6. Greshock, T. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 2643.
7. Huntley, R. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3403.
8. (a) Yuecel, B.; Arve, L.; de Meijere, A. *Tetrahedron* **2005**, *61*, 11355; (b) Pross, A.; Sternhill, S. *Aust. J. Chem.* **1970**, *23*, 989.
9. Overman, L. E.; Mendelson, L. T.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629.
10. Burk, M. J.; Lee, J. R.; Martinez, J. P. *J. Am. Chem. Soc.* **1994**, *116*, 10847.
11. Tang, W.; Zhang, X. *Angew. Chem. Int. Ed.* **2002**, *41*, 1612.
12. Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.
13. Van den Berg, M.; Haak, R. M.; Minnaard, A. J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Adv. Synth Catal.* **2002**, *344*, 1003.
14. Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870.