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A Flexible, Convergent Approach to Polycyclic Indole Structures: Formal Synthesis of (±)-Mersicarpine

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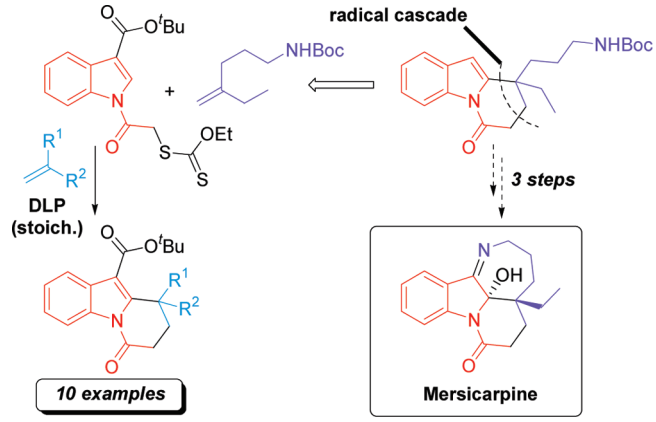
ABSTRACT



The formal synthesis of (±)-mersicarpine was achieved using an intermolecular radical addition−radical cyclization cascade. This key reaction represents a flexible, convergent route to numerous polycyclic indole derivatives.

Mersicarpine **1** was isolated in 2004 by Kam and co-workers[1] from the *Kopsia* species of plants, which contains a large range of alkaloids with challenging carbon frameworks. This unusual tetracyclic compound is part of a class of indole alkaloids bearing a six-membered ring fused to the 1,2-positions and containing a typical quaternary center (Figure 1).

The first total synthesis of mersicarpine **1** was reported by Kerr et al. in 2008.[2] Inspired by his original strategy, we envisaged the obtention of key intermediate **4** by a different, but simpler and more convergent, route. Our synthetic approach to structure **1** is based on a radical cascade, whereby radical species **5** undergoes first an intermolecular addition onto the double bond of olefin **6** followed by a cyclization on the 2-position of the indole ring (Scheme 1). Subsequent conversion of indole **4** into mersicarpine **1** through oxidation and formation of the 7-membered ring imine were reported by Kerr et al. and proceed in good yield.[2]

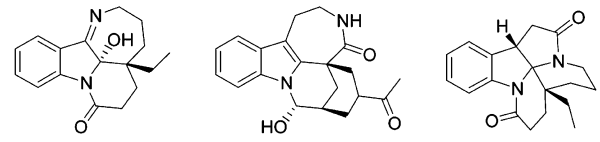


Figure 1. Indole alkaloids from *Kopsia* species.

In a preliminary study,[3] xanthate **7** was easily prepared via the acylation of indole with chloroacetyl chloride

(1) Kam, T. S.; Subramaniam, G.; Lim, K. H.; Choo, Y. M. *Tetrahedron Lett.* **2004**, *45*, 5995.
(2) Magolan, J.; Carson, C. A.; Kerr, M. A. *Org. Lett.* **2008**, *10*, 1437.
(3) Seguin, S. Ph.D. Dissertation, Ecole Polytechnique, Palaiseau, 1999.

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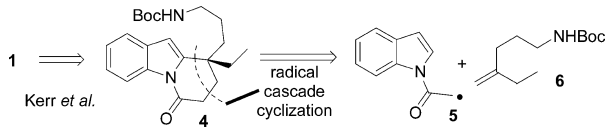
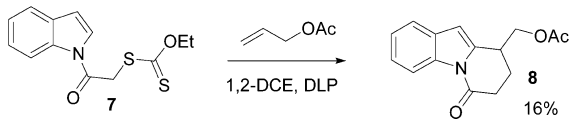
Scheme 1. Retrosynthesis of Mersicarpine **1**



followed by nucleophilic substitution of the chlorine atom by potassium *O*-ethyl xanthate salt. Previous works in this field indicated that cyclization should occur regioselectively at the 2-position of the indole ring.[2,4]

However, portionwise addition of lauroyl peroxide (DLP) to xanthate **7** and several equivalents of allylacetate in refluxing 1,2-dichloroethane gave rise to only a very poor yield of desired cyclic compound **8** (Scheme 2).[5]

Scheme 2

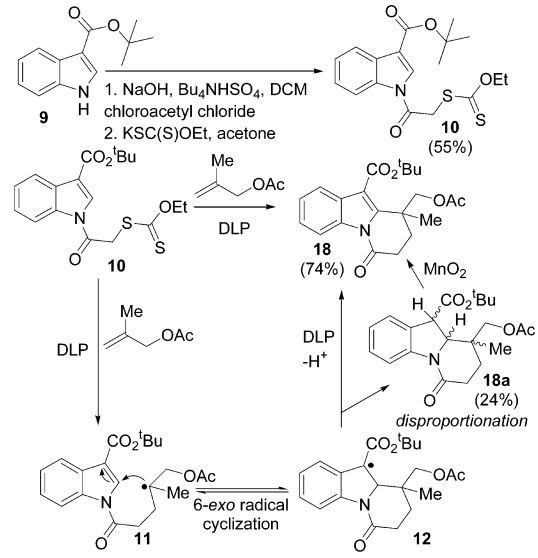


These disappointing results led us to examine the effect of activating the indole double bond by a functional group that could be subsequently removed. To this end, xanthate **10** bearing an electron-withdrawing *tert*-butoxycarbonyl group in the 3-position was prepared[6] from *tert*-butylindole-3-carboxylate **9**, which is readily available by treatment of indole-3-carboxylic acid with oxalyl chloride, followed by exposure of the intermediate acid chloride to potassium *tert*-butoxide in *t*-butyl alcohol.[7]

When a stoichiometric amount of DLP was added in portions (over 1−2 h) to a refluxing solution of **10** and methallyl acetate (5 equiv) in chlorobenzene, addition to the olefin and subsequent annelation to the 2-position of the indole ring took place to give **18** in 49% yield, along with a mixture of diastereoisomers (**18a**, 24%), arising from the premature reduction of radical species **12**. Once the total consumption of xanthate was observed, the crude reaction mixture of cyclized products was therefore heated with excess manganese dioxide (MnO_2, 10 equiv) to completely aromatize **18a** into the desired indole **18** (74%).

Addition of the radical derived from xanthate **10** to methallyl acetate furnishes intermediate **11**, which then undergoes a 6-*exo* cyclization to the indole ring. The ensuing radical **12** is now stabilized by the *tert*-butyl ester group, and this extra favorable factor drives the equilibrium in the crucial step forward.[8] Disproportionation of radical **12** leads presumably to compounds **18** and **18a**. The former can also be produced by electron transfer to the peroxide, accounting for its higher relative yield (Scheme 3).

Scheme 3. Preparation of Xanthate **10** and Mechanism of the Cascade Cyclization



The same sequence was applied to other olefins to give tricyclic derivatives **13**−**22** in comparable overall yield (Table 1). The results shown in Table 1 are uniformly good. This process can thus be applied to a large variety of terminal olefins bearing various types of substituents. Even polymerization-prone methyl acrylate could be used (entry 5), although the yield was slightly lower than average. In this case, the kinetics of the cascade reaction seem to be fast enough to circumscribe the untoward tendency to polymerization of methyl acrylate.To expand the scope of the reaction, the analogous cyclizations using xanthate derivatives of commercially available indole-3-acetic acid,[9] indole-3-carboxaldehyde, and 3-acetylindole were next investigated.

(4) (a) Reyes-Gutiérrez, P. E.; Torres-Ochoa, R. O.; Martínez, R.; Miranda, L. D. *Org. Biomol. Chem.* **2009**, *7*, 1388. (b) Guerrero, M. A.; Miranda, L. D. *Tetrahedron Lett.* **2006**, *47*, 2517. (c) Osornio, Y. M.; Cruz-Almanza, R.; Jiménez-Montaño, V.; Miranda, L. D. *Chem. Commun.* **2003**, 2316. (d) Magolan, J.; Kerr, M. *Org. Lett.* **2006**, *8*, 4561. (e) Gross, S.; Reissig, H. U. *Org. Lett.* **2003**, *5*, 4305.

(5) For reviews of the xanthate transfer chemistry, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672. (b) Zard, S. Z. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH; Weinheim 2001, Vol. 1, p 90. (c) Quiclet-Sire, B.; Zard, S. Z. *Chem.—Eur. J.* **2006**, *12*, 6002. (d) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (e) Zard, S. Z. *Org. Biomol. Chem.* **2007**, *5*, 205.

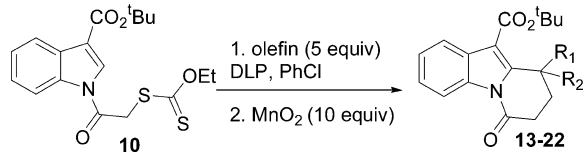
(6) (a) Coste, A.; Toumi, M.; Wright, K.; Razafimahaléo, V.; Couty, F.; Marrot, J.; Evano, G. *Org. Lett.* **2008**, *10*, 3841. (b) Toumi, M.; Couty, F.; Marrot, J.; Evano, G. *Org. Lett.* **2008**, *10*, 5027.

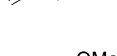
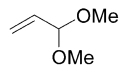
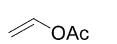
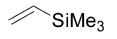
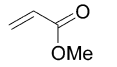
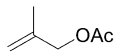
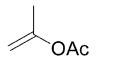
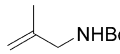
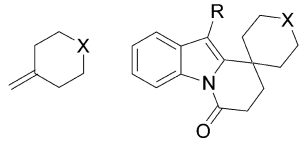
(7) (a) Janosik, T.; Shirani, H.; Wahlström, N.; Malky, I.; Stensland, B.; Bergman, J. *Tetrahedron* **2006**, *62*, 1699. (b) Ludwig, J.; Lehr, M. *Synth. Commun.* **2004**, *34*, 3691. (c) Battaglia, S.; Boldrini, E.; Da Settimo, F.; Dondio, G.; La Motta, C.; Marini, A. M.; Primofiore, G. *Eur. J. Med. Chem.* **1999**, *34*, 93. (d) Stanovnik, B.; Tišler, M.; Carlock, J. T. *Synthesis* **1976**, 754.

(8) The addition of radicals to aromatic rings is known to be reversible. See: (a) Citterio, A.; Minisci, F.; Porta, O.; Sesana, G. *J. Am. Chem. Soc.* **1977**, *99*, 7960. (b) Griller, D.; Marriott, P. R.; Nonhebel, D. C.; Perkins, M. J.; Wong, P. C. *J. Am. Chem. Soc.* **1981**, *103*, 7761. The reverse reaction, i.e., the fragmentation of the cyclohexadienyl radicals, has been elegantly applied in synthesis. For a review, see: (c) Walton, J. C.; Studer, A. *Acc. Chem. Res.* **2005**, *38*, 794.

(9) For the preparation of the corresponding methyl ester, see: Časar, Z.; Bevk, D.; Svete, J.; Stanovnik, B. *Tetrahedron* **2005**, *61*, 7508.

Table 1. Annulation Sequence of Indole Xanthate **10**



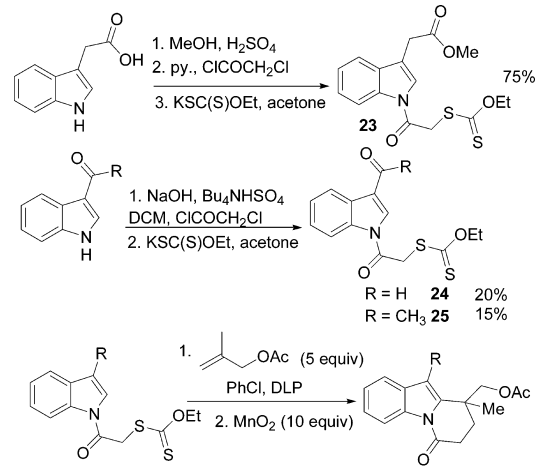
entry	olefin		product	yield (%)
1		**13**	R^1 = CH_2OAc R^2 = H	69 (49)[a]
2[b]		**14**	R^1 = $CH(OMe)_2$ R^2 = H	57
3		**15**	R^1 = OAc R^2 = H	75
4		**16**	R^1 = $SiMe_3$ R^2 = H	65
5[b]		**17**	R^1 = CO_2Me R^2 = H	44
6		**18**	R^1 = CH_2OAc R^2 = Me	74 (49)[a]
7		**19**	R^1 = OAc R^2 = Me	70
8		**20**	R^1 = CH_2NHBoc R^2 = Me	63
9		**21** **22**	X = CH_2 X = NBoc	75 79

[a] Yield without MnO_2 oxidation. [b] PhCl was replaced by 1,2-DCE.

Xanthates **23**−**25** were prepared by acylation of the corresponding indoles with chloroacetyl chloride followed by chloride displacement with potassium *O*-ethyl xanthate. Access to **24** and **25** proved more troublesome than for **10** and **23**. Nevertheless, all three derivatives turned out to be good precursors for the radical cyclization with methallyl acetate (Scheme 4).

These results indicate that 3-acetyl, 3-carboxyaldehyde, or even a $-CH_2CO_2Me$ group are compatible with the process, extending the potential field of the reaction to a wider spectrum of available indole precursors (tryptamine, tryptophan, etc.).[4a] The important factor appears to be the presence of a substituent on position 3 of the indole that

Scheme 4. Preparation of Xanthates **23**−**25** and Synthesis of Corresponding Tricyclic Compounds



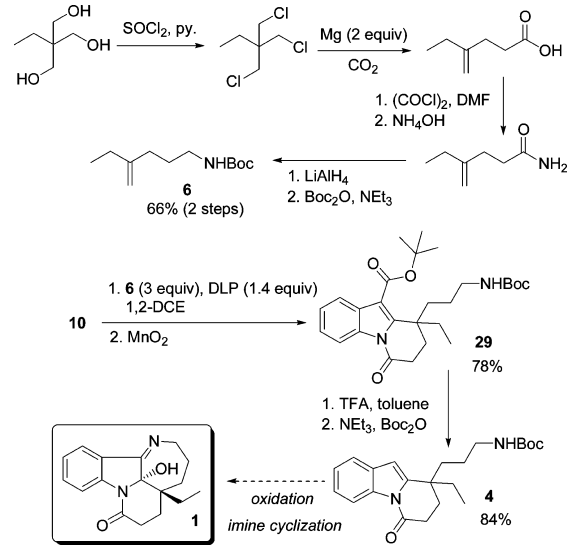
entry	xanthate		product	yield
1[a]	**23**	R = CH_2CO_2Me	**26**	53%
2	**24**	R = CHO	**27**	45%
3	**25**	R = Ac	**28**	64%

[a] PhCl was replaced by 1,2-DCE; single addition of DLP (1.4 equiv); no MnO_2 oxidation was required.

stabilizes the radical intermediate and/or facilitates its oxidation by the peroxide.

With a good cyclization process in hand, we proceeded to construct *N*-acyl indole **4**, the key intermediate reported by Kerr et al. in their elegant synthesis of mersicarpine **1**.[2] To this end, olefin **6** was prepared according to a procedure[10a] previously used in the synthesis of the indole alkaloid aspidospermidine by Magnus and co-workers.[10b] This olefin

Scheme 5. Preparation of Olefin **6** and Formal Synthesis of (±)-Mersicarpine



(10) (a) McCaffery, E. L.; Shalaby, S. W. *J. Organomet. Chem.* **1967**, *8*, 17. (b) Exon, C.; Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 4739.

(11) It may be interesting to replace the *tert*-butoxycarbonyl group in **10** with a carboxamide derived from a non-racemic chiral amine, as this may allow control of the absolute stereochemistry in the cyclization step.

contains both the ethyl and the protected amino groups required for the synthesis of mersicarpine. Pleasingly, the radical cascade of xanthate **10** and olefin **6** proceeded normally to afford **29** in good yield (78%). A one-pot deprotection of the *tert*-butyl ester group and decarboxylation were performed in trifluoroacetic acid, followed by subsequent reprotection of the amine as its *tert*-butyl carbamate to give **4** in 84% yield (Scheme 5). This completes the formal synthesis of mersicarpine **1**.[11]

In summary, we have developed a simple convergent and flexible route to polycyclic indole derivatives bearing various functional groups. These could prove to be useful new scaffolds for medicinal chemistry. The fact that an acetate group can be present on the indole partner (as in compound **26**) indicates that the same strategy employed for the synthesis of mersicarpine could be applied to the construction of leuconoxine **3** and, with some variation, to tronocarpine **2**.

Acknowledgment. We respectfully dedicate this paper to Professor E. J. Corey (Harvard University). A.B. thanks Ecole Polytechnique for a studentship.

Supporting Information Available: Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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