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STUDIES ON ENOL CARBONATE CHEMISTRY: STEREOSELECTIVE CONSTRUCTION OF VICINAL QUATERNARY BENZYLIC CENTERS IN THE BIS-OXINDOLE SERIES‡

Candice Menozzi, Peter I. Dalko*§ and Janine Cossy

Laboratoire de Chimie Organique associé au CNRS, ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05 - France;

Fax: +33 (0)140794660; e-mail: peter.dalko@univ-paris5.fr

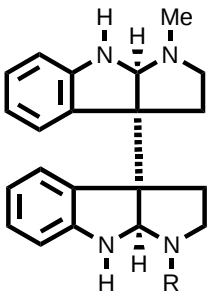
Abstract - The Steglich-type intramolecular acyl transfer of bis-oxindole enol carbonate derivatives **9a**-**c** affords selectively the monorearranged products **11a**-**c**. In turn, Pd(0)-mediated allyl transfer of the bis-Alloc derivative **9c** allows an efficient double *C*-allylation leading preferentially to the *d*/*l* isomer.

INTRODUCTION

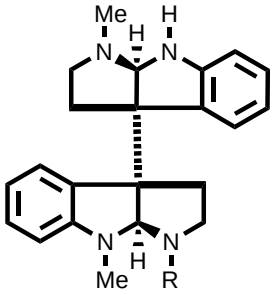
The synthesis of natural products having contiguous quaternary benzylic centers remains one of the most challenging problems in organic chemistry.[1,2] Recently, we described a short synthesis of N_b-desmethyl-*meso*-chimonanthine **2** possessing desymmetrized hexacyclic 3a,3a'-bis-pyrrolidinoindoline skeleton.[3] Members of the *Calycanthaceous* alkaloid family,[4] such as chimonanthines[5,6] **1** and **3** or the more complex leptosins[7] **4**, and verticillins[8] **5** exhibit promising biological activity (Figure 1). Indeed, (*d*)-chimonanthine **3** shows analgesic activity[9] whereas antimicrobial,[8a] antinemodal activity[8c] against *Caenorhabditis elegans* and *Panagrellus redivivus* as well as cytotoxic activity are observed for verticillins.[10] Leptosins possess significant antitumour activity against the murine P388 cell line[7] and in addition, leptosin M shows cytotoxic activities against 39 human cancer cell lines.[7a]

‡ This article is dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday.

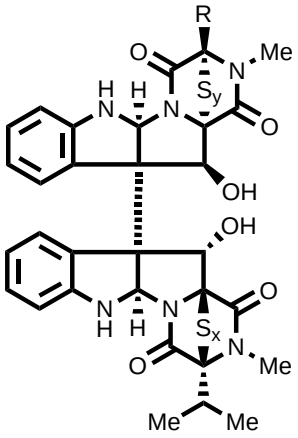
§ Current address: Laboratoire de Chimie et de Biochimie Pharmacologique et Toxicologique, Université René Descartes, 75270 Paris Cedex 06, France.



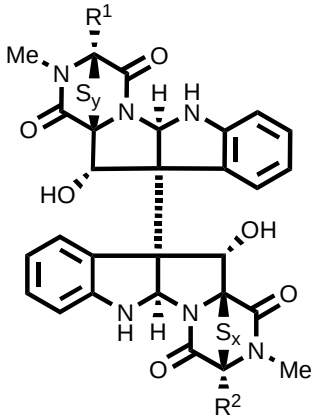
1 R = Me *meso*-chimonanthine
2 R = H N_b-desmethyl-*meso*-chimonanthine



3 (*d*)-chimonanthine



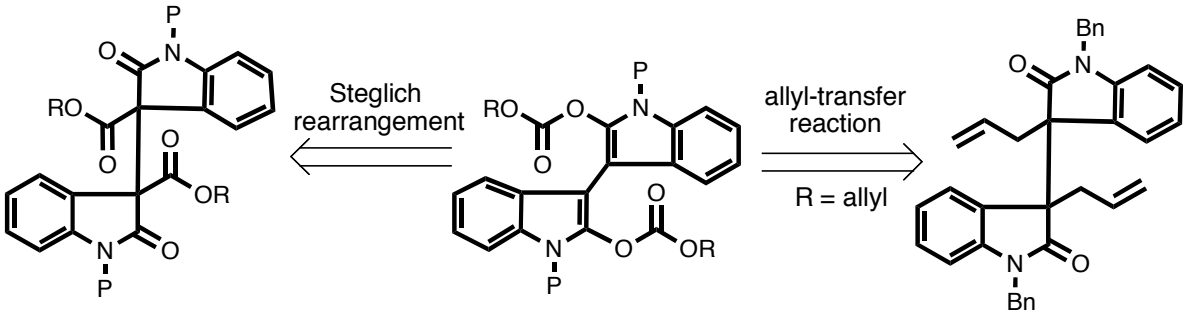
4a leptosin G x = 3, y = 4, R = CH_2OH
4b leptosin K x = 2, y = 2, R = *i*-Pr



5a verticillin A x = y = 2, $R^1 = R^2 = CH_3$
5b verticillin D x = y = 2, $R^1 = R^2 = CH_2(OH)CH_3$

Figure 1. Naturally occuring bis-pyrrolidinoindoline alkaloids.

The synthetic access to bis-pyrrolidinoindoline alkaloids requires a flexible strategy allowing the preparation of both the *meso* and the optically active (*d*/*l*) skeleton. Considering the inherent symmetry propriety of the molecules, a bidirectionnal synthesis allowing the simultaneous control of the C-3a and C-3a' stereogenic centers in 3a,3a'-bispyrrolodino[2,3-*b*]indoline unit seemed to be the most appealing.



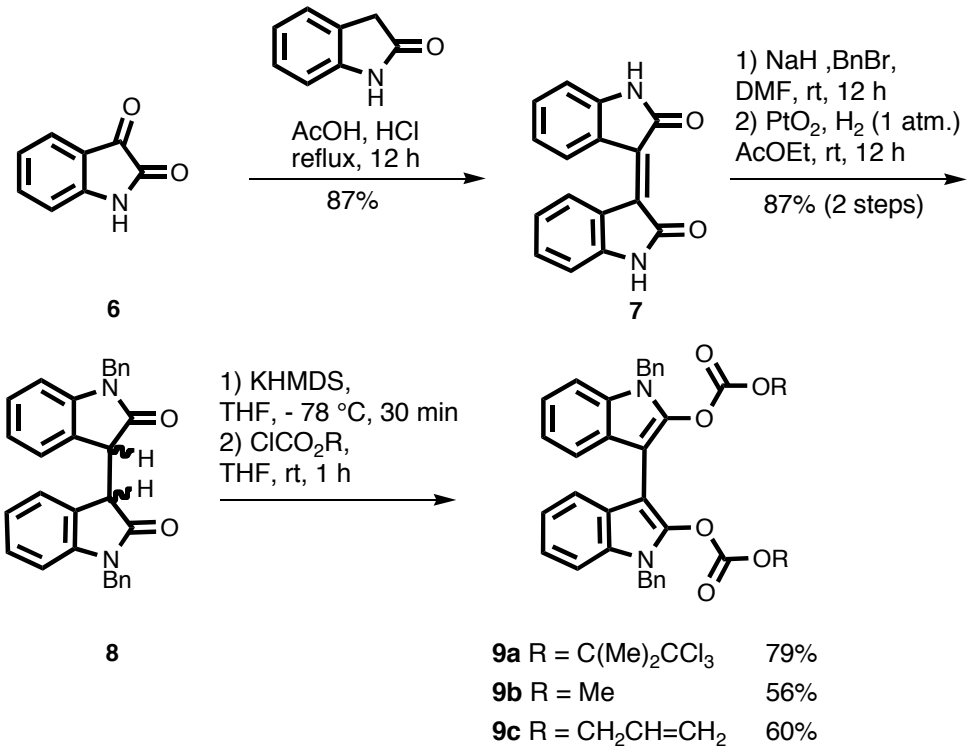
P = protecting group

Figure 2. Bidirectional strategy in preparing functionalized bis-oxindole skeleton having vicinal quaternary benzylic centers.

We speculated, that an intramolecular acyl transfer, or allyl transfer may overcome the inherent low reactivity of the benzylic/neopentylic centers, and may also be amenable for sequential transformations. Here, we wish to report our results concerning the Steglich acyl rearrangement of bis-enol carbonates derived from bis-oxindoles, and also the Pd(0)-catalyzed allyl transfer in Alloc derivatives (Figure 2).

RESULTS AND DISCUSSION

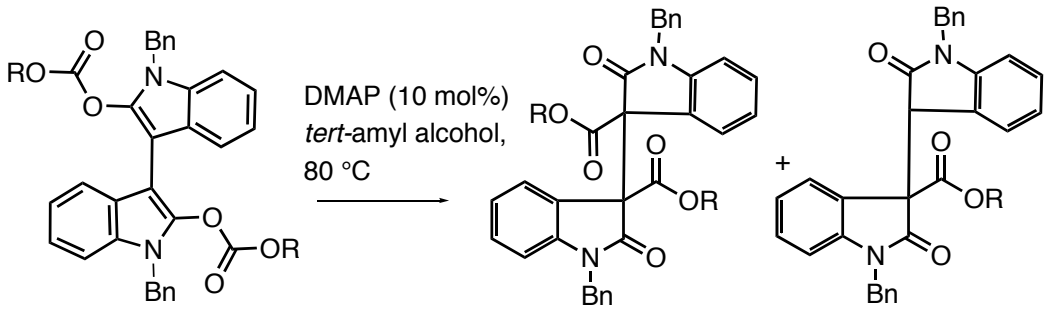
Electron rich *O*-acylated oxazolinones can be transformed to the corresponding *C*-acylated products in the presence of acyl transfer catalysts, such as DMAP.[11] One advantage of this methodology appeared to be that the reaction is amenable under asymmetric conditions as enantioselective versions of this reaction were developed using chiral DMAP derivatives,[12] *N*-heterocyclic carbene[13] metallocene-pyrrolidinopyridine[14] as catalysts. By using a double Steglich rearrangement, the two quaternary centers of the axially symmetric *d*/*l*-chimonanthine core would be controlled from intermediate **9** (Scheme 1). A close analogy, reported recently in the 3-methyl oxindole series[12] encouraged us to consider the feasibility of such a double rearrangement.



Scheme 1. Synthetic sequence for the preparation of bis-enol carbonates **9a**-**c**.

For this study the protected bis-oxindole **8**, was prepared in 3 steps (Scheme 1). At first, isatin **6** and oxindole were condensed under acidic conditions (AcOH, HCl, reflux)[15] to produce isoindigo **7** in 87% yield. After bis *N*-benzylation (NaH, BnBr, DMF)[4a] followed by hydrogenation of the olefin on platinum oxide,[16] bis-oxindole **8** was isolated in 87% yield. The required bis-enol esters were prepared by treatment of **8** with KHMDS at –78 °C and the bis-enolates were quenched with chlorocarbonates such as *β,β,β*-trichloro-*tert*-butyl chloroformate (TcBoc-Cl), methyl chloroformate ($ClCO_2Me$) and allyloxycarbonyl chloride (Alloc-Cl), leading to **9a** (79%), **9b** (56%) and **9c** (60%), respectively. The obtained compounds were stable and were purified by chromatography on silica gel. This short and efficient sequence allowed the isolation of the enol carbonates required for the Steglich rearrangement.

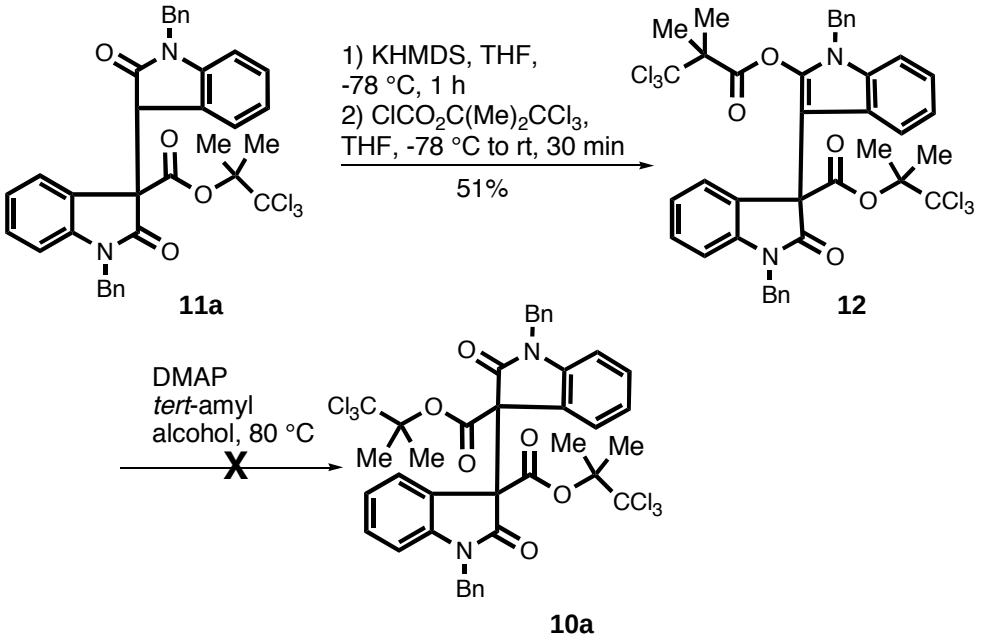
Different conditions for the Steglich rearrangement were applied to compounds **9a**-**c**. The best results were obtained in the presence of DMAP (10 mol%) in *tert*-amyl alcohol at 80 °C (Scheme 2). Under these conditions, a rapid mono-rearrangement took place and compounds **11a**-**c** were isolated in 83%, 85% and 43% yields, respectively (Scheme 2). Unfortunately, no conditions, allowing the double rearrangement were found.



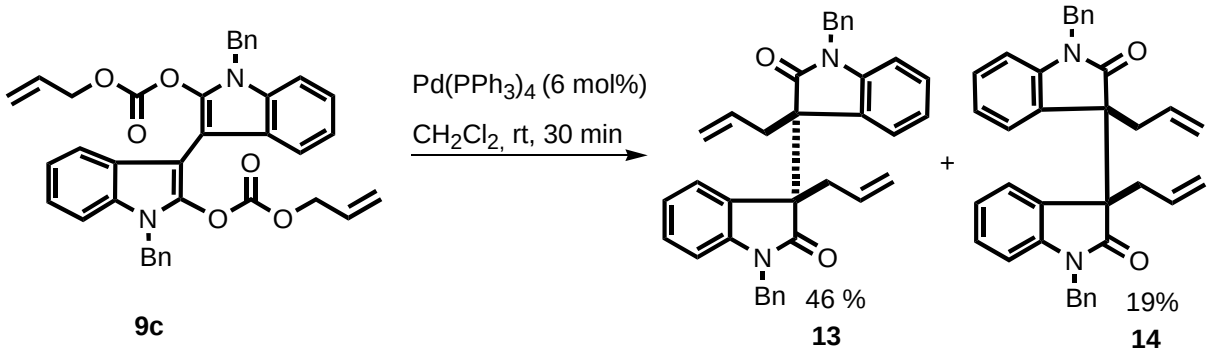
9	Reaction Time	**10**	**11**
a R = $C(Me)_2CCl_3$	30 min	0%	83%
b R = Me	1 h	0%	85%
c R = $CH_2CH{=}CH_2$	1 h	0%	43%

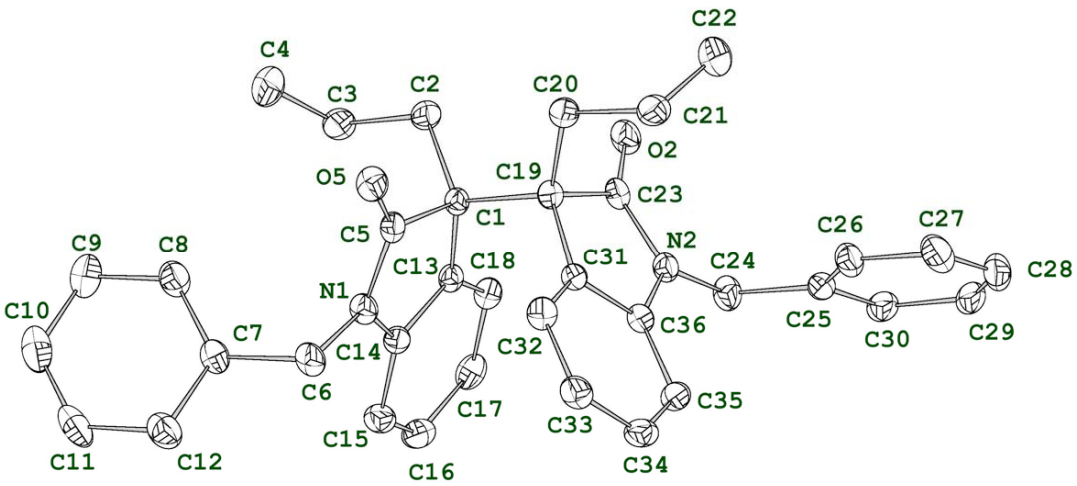
Scheme 2. Steglich rearrangement applied to compounds **9a**-**c**.

Moreover, when the Steglich conditions (DMAP, *tert*-amyl alcohol) were applied to enol carbonate **12** (Scheme 3), prepared from the mono-rearranged oxindole **11a** (KHMDS, $ClCO_2C(Me)_2CCl_3$ at –78 °C), no acyl transfer was observed and the only isolated product was compound **11a**, formed by the loss of the enol carbonate appendage. This result indicated, that the combination of steric and electronic factors may compromise the formation of the second quaternary center.



Scheme 3. Reiteration of the Steglich rearrangement of enol carbonate **12**.





Scheme 4. Allyl transfer reaction of the bis-Alloc derivative **9c**.

As alternative strategy, allyl transfer of the bis-Alloc enolate **9c** was examined under Stoltz's conditions.[17] Under these conditions a fast *O*- to *C*-allyl transfer was observed, in CH_2Cl_2 at room temperature in the presence of a catalytic amount of $Pd(PPh_3)_4$ (6 mol%) and the reaction provided the two diastereoisomers **13** and **14** in 46% and 19% yields, respectively (Scheme 4). Products were separated by chromatography on silica gel, and the structure of the major isomer was established by X-ray analysis, and revealed to be the *d*/*l* isomer **13**.

In summary, the DMAP-mediated intramolecular acyl transfer of bis-oxindole enol carbonates **9a**-**c** under Steglich's conditions afforded selectively esters **11a**-**c** which correspond to the mono-rearranged products. The Pd(0)-mediated allyl transfer of the bis-Alloc derivative **9c** created simultaneously two adjacent quaternary benzylic stereogenic centers, leading preferentially to the *d*/*l* isomer. Further studies of this transformation allowing the selective preparation of the optically active isomers are currently underway and will be reported in due course.

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