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Total Synthesis of Macrocarpines D and E via an Enolate-Driven Copper-Mediated Cross-Coupling Process: Replacement of Catalytic Palladium with Copper Iodide

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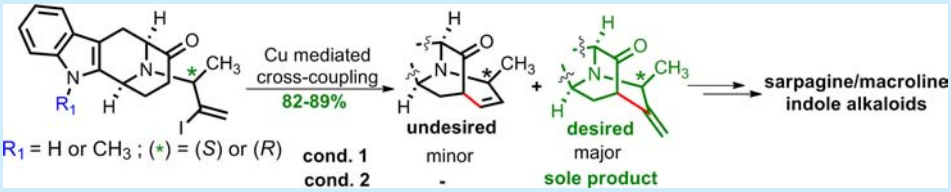
Supporting Information



ABSTRACT: An enolate driven copper-mediated cross-coupling process enabled cheaper and greener access to the key pentacyclic intermediates required for the enantiospecific total synthesis of a number of C-19 methyl substituted sarpagine/macroline indole alkaloids. Replacement of palladium (60−68%) with copper iodide (82−89%) resulted in much higher yields. The formation of an unusual 7-membered cross-coupling product was completely inhibited by using TEMPO as a radical scavenger. Further functionalization led to the first enantiospecific total synthesis of macrocarpines D and E.

The medicinal plants of the *Alstonia* (Apocynaceae) genus have been used in traditional medicine in many countries of the world from antiquity.[1] Their traditional uses include treatment of ulcers, dysentery, malaria, anthelmintics, diabetes, rheumatism, snake bites, etc.[1] Indole alkaloid secondary metabolites of these plants are the most probable source of their medicinal activity.[2] According to a review by Cordell et al., among the 60 plant-derived alkaloids of medicinal significance, 39 were directly related to their traditional uses.[3] Macroline/sarpagine-type indole alkaloids are one of the major classes of alkaloids isolated from these species to date by Le Quesne, Elderfield, Schmid, Kam, and others.[4−7] Macrocarpine A-C (**1**−**3**) were isolated from the bark extract of *Alstonia macrophylla* in 2004.[8] Several other alkaloids of the same series, macrocarpine D (**4**) and macrocarpines E−H (**5**−**8**), were isolated in 2014 from the stem-bark and leaf extracts of *A. macrophylla* and *A. angustifolia*, respectively, by Kam et al.[9,10] All of these macroline type indole alkaloids, macrocarpines A−H (**1**−**8**), share the common feature of a *β*-methyl substituent at the C-19 position. This is a distinct difference from previous *Alstonia* alkaloids isolated by Le Quesne and Schmid.[5,7] To date, around 30 alkaloids of the sarpagine/macroline/ajmaline family, which bear a diastereomeric methyl function at C-19, have been isolated.[4,11] Macroline related alkaloids *N*(4)-methyl-*N*(4),21-secotalpinine (**9**),[8,12] *N*(4)-methyltalpinine (**10**),[12] and 19-epitalcarpine (**11**)[10] as well as sarpagine related alkaloids macrosalhine chloride (**12**)[13] and deoxyperaksine (**13**)[14] also possess the C-19 methyl substitution. Among these, **11** and **13** have a diastereomeric *α*-methyl group at C-19. The synthesis of these alkaloids (**1**−**13**, Figure 1) has not been reported yet. Moreover, *N*(4)-methyltalpinine (**10**) and *N*(4)-methyl-*N*(4),21-secotalpinine (**9**) have been reported recently to have potent anticancer (NF-*κ*B inhibitor, ED_{50} 1.2 *μ*M) activity and profound leishmanicidal[12] activity, respectively. The unique structural features and potential medicinal properties prompted attempts at the first total synthesis of this class of alkaloids via a general strategy for the entire series. This is the basis of the approach toward chemical economy described here.

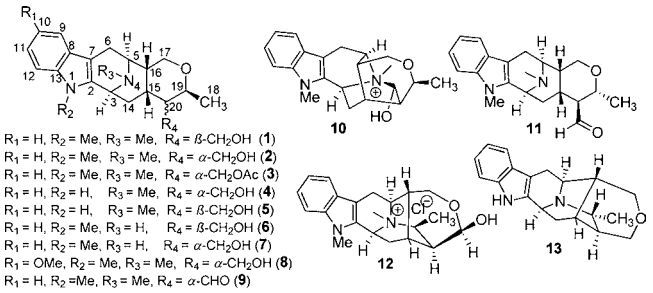


Figure 1. Examples of some C-19 methyl-substituted sarpagine/macroline indole alkaloids.

Copper-mediated carbon−carbon bond formation is more than a century old.[15] Although palladium-catalyzed cross-

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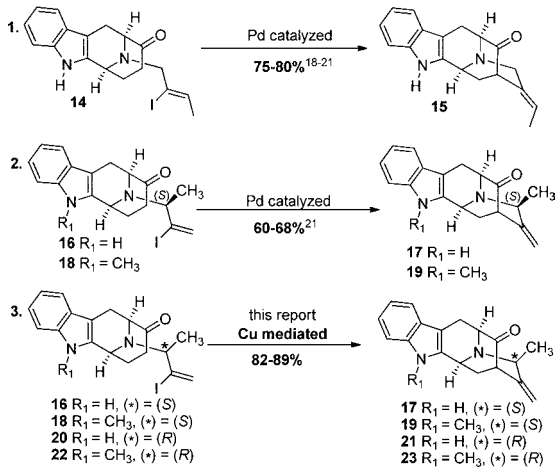
coupling reactions have been the dominant method in the field of total synthesis of complex natural products, copper has proven itself to be an essential alternative, as indicated by the increase in copper-mediated cross-coupling processes over the last decade.[16] As a result, it was decided to investigate a copper-catalyzed or -mediated coupling process to offer a less expensive and less toxic alternative to catalytic palladium while avoiding phosphine-based ligand for easier purification. Moreover, potential improvements in yields as well as workup and purification would be important.[17]

Wang et al.[18] developed an enolate-driven palladium-catalyzed α-vinylation of a ketone in 2000 (Scheme 1, entry 1). This

Scheme 1. Regiospecific Access to the Pentacyclic Core System via Palladium- and Copper-Catalyzed Cross-Coupling Process

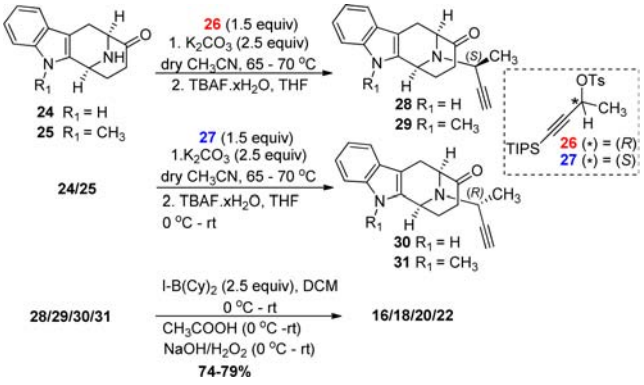


process has been employed in the total synthesis of several sarpagine/macroline/ajmaline indole alkaloids.[19−21] Although this palladium-catalyzed process was effective in accessing the key intermediate **15** from vinyl iodide **14**, it provided only 60−68% yield in the case of vinyl iodides **16** or **18** (Scheme 1, entry 2), wherein there was a diastereomeric methyl function along with a terminal olefin in place of the ethylidene function in **14** (internal olefin[18]). These features in **16** and **18** make them structurally and chemically different from **14**. Since the diastereomeric methyl function was essential for the synthesis of C-19 methyl-substituted alkaloids, further improvement was required for better access to the key intermediates **17**, **19**, **21**, and **23**. More importantly, replacement of palladium with the cheaper and less toxic copper would greatly facilitate use of this enolate-mediated process by others, and formed much of the driving force in this research.

The copper-catalyzed conditions[22] that has been used for the α-vinylation of **14** gave lower yields along with an unusual, undesired product in the case of **22** (Scheme 3). Numerous attempts were made to optimize the desired yield of the olefin **23**, eliminate the unusual side product **23′**, and understand the mechanism of multiple competing reactions. The implementation, improvement, and extension of the scope of this process to access the C-19 methyl-substituted sarpagine/macroline/ajmaline alkaloids with either an (*R*) or (*S*) C-19 methyl substituent in the N_a-H as well as N_a-CH_3 series (Scheme 1, entry 3) form the basis of this communication.

All of the vinyl iodide intermediates (**16**, **18**, **20**, and **22**) were prepared according to the previously reported procedures[21] (Scheme 2) beginning from the tetracyclic ketones **24**/**25**, which

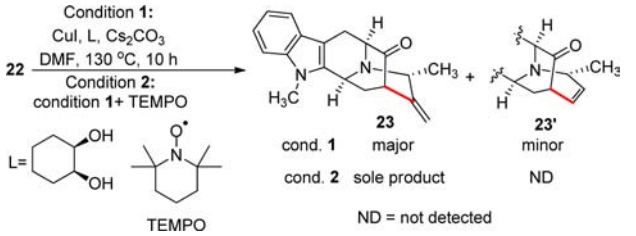
Scheme 2. Completely Regioselective Access to the Vinyl Iodides 16, 18, 20, and 22



had been prepared in the standard two-pot process on a 300 g scale.[23] As depicted in Scheme 2, the N_b alkylation via S_N2 substitution of the chiral tosylates (**26**/**27**) in CH_3CN with K_2CO_3 and subsequent deprotection of the TIPS protecting group with wet TBAF in THF furnished the N_b-alkylated terminal alkynes (**28**−**31**) in excellent yields. Haloboration[21] of the terminal alkynes with I−B(Cy)$_2$ in DCM followed by protodeboronation with HOAc resulted in the vinyl iodides (**16**, **18**, **20**, and **22**) in 74−79% yield with complete regioselectivity.

Initial experiments with vinyl iodide (**22**) and CuI under the reported conditions[22] resulted in the desired product (**23**) in lower yields (∼42%) along with an unusual/unexpected cyclization product (**23′**), a seven-membered ring with an internal alkene (Scheme 3).

Scheme 3. Enolate-Driven Copper-Mediated Cross-Coupling of the Vinyl Iodide (22)



The structures of both the desired (**23**) and unexpected seven-membered ring (**23′**) cross-coupling products have been confirmed by MS, 1D and 2D NMR, and X-ray crystallographic analysis (see the Supporting Information for details). In the absence of CuI, the same conditions yielded the seven-membered product to a greater extent. Increasing the equivalents of CuI and ligand to 1.0 equiv and the base to 4.0 equiv (entry 3 of Table 1) resulted in a higher overall yield of the desired material (67%), while the unexpected product was still present (∼21%).

It was not surprising that this series of vinyl iodides (**16**, **18**, **20**, and **22**) would have different reactivities than vinyl iodides reported earlier.[18] Differences in the substrates included the presence of a methylidene (a terminal alkene) instead of the ethylidene in **14** (an internal alkene) as well as the presence of the chiral methyl function at C-19 instead of an achiral methylene. In order to rationalize this unprecedented seven-membered ring cyclization, it was felt that a radical mechanism may have been involved in its formation. To test this hypothesis, it was decided to use 2,2,6,6-tetramethylpiperidinyl-1-oxy

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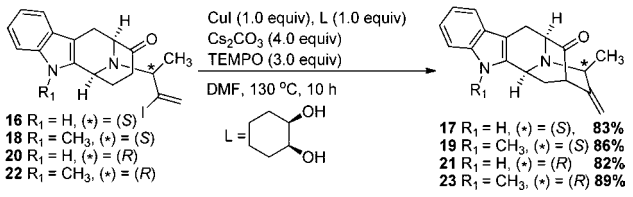
Table 1. Optimization of Reaction Conditions for the Cu-Mediated Cross-Coupling Reaction of 22

entry	CuI or cat. (equiv)	L (equiv)	Cs_2CO_3 (equiv)	scv[a] (equiv)	23:23′ (by NMR)[b]	overall yield[c] (%)
1	0.5	0.5	2.0		89:11	47
2		0.5	2.0		63:37	45
3	**1.0**	**1.0**	**4.0**		**79:21**	**67**
4			2.0		64:36	35
5	0.5	0.5	2.0	2.5	97:3	45
6	**0.5**	**0.5**	**2.0**	**3.0**	**100:0**	**66**
7	**1.0**	**1.0**	**4.0**	**3.0**	**100:0**	**89**
8	0.1	0.1	4.0	3.0	100:0	25
9	0.5	0.5	4.0	3.0	100:0	40
10	1.0		4.0	3.0	100:0	11
11	1.0	1.0		3.0		ND[d]
12		1.0	4.0	3.0		ND
13	cat.-2 (1.0)	1.0	4.0	3.0	100:0	51
14	cat.-3 (1.0)	1.0	4.0	3.0	100:0	24
15	cat.-4 (1.0)	1.0	4.0	3.0	100:0	28

[a]scv = TEMPO scavenger. [b]Ratio determined by ^{1}H NMR spectroscopy. [c]Overall isolated yield after flash chromatography on neutral alumina. [d]Starting material was recovered; ND = not detected; L = *cis*-1,2-cyclohexanediol; cat.-2 = $Cu(CH_3CN)_4ClO_4$; cat.-3 = $Cu(CH_3CN)_4PF_6$; cat.-4 = $Cu(CH_3CN)_4OTf$ (see the SI for detailed experimental procedures).

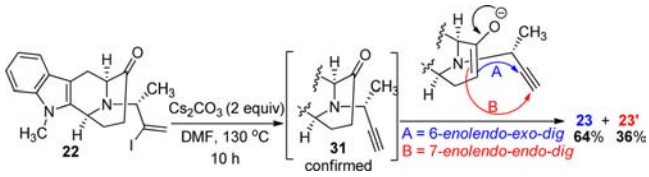
(TEMPO), the well-known radical scavenger,[24] to inhibit any radical step or species that may have diverted the mechanism. In support of this hypothesis, an experiment with 2.5 equiv of TEMPO (entry 5 of Table 1) resulted in almost complete inhibition of the formation of the undesired 7-membered internal alkene (~3% by NMR spectroscopy) with 45% overall yield of **23**. Increasing the amount of TEMPO to 3.0 equiv completely eliminated the undesired cyclization (see the SI) and provided the desired cross-coupling product **23** in 66% yield. After many experiments with different reaction parameters and screening different copper sources (entries 8−15 of Table 1), the optimized conditions were found to be 1.0 equiv of CuI, 1.0 equiv of ligand, 4.0 equiv of Cs_2CO_3, and 3.0 equiv of TEMPO. This combination furnished 89% yield of the desired cross-coupled product to the exclusion of the 7-membered byproduct as compared to 60−68% with a palladium catalyst.[21,25] This modified reaction condition was effective for both stereoisomers of the C-19 methyl substitution and in both the N_a-H and N_a-CH_3 series (**16**, **18**, **20**, and **22**) as well. This permitted the application of this Cu-mediated cross-coupling process to access the key intermediates (**17**, **19**, **21**, and **23**) in gram quantities toward all of the macroline/sarpagine alkaloids discussed above (Scheme 4). While TEMPO was initially chosen as a radical probe, the reason for its useful effect is under investigation.

Scheme 4. Access to the Key Pentacyclic Ketone Intermediates 17, 19, 21, and 23 via the Optimized Conditions



Surprisingly, it was observed that the base Cs_2CO_3 alone in DMF (entry 2 of Table 1) could yield both of the products in an approximately 2−1 ratio. This observation indicated the possibility of another competing mechanism wherein the vinyl iodide (**22**) or intermediate underwent an E-2-like elimination or radical process to produce a terminal alkyne (**31**, in situ). This alkyne subsequently could undergo a 6-(*enolendo*)-*exo-dig* (process A in Scheme 5) which would produce the six-membered

Scheme 5. Possible Mechanism for the Observed Base Mediated Cyclization (Table 1, Entries 2 and 4)

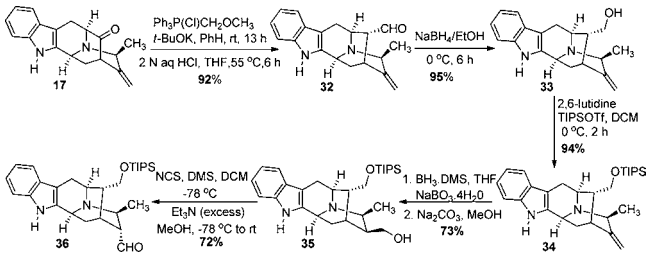


external alkene (**23**) as a major product and a 7-(*enolendo*)-*endo-dig* cyclization (process B in Scheme 5) to produce the seven-membered internal alkene (**23′**) as the minor product (Scheme 5). Both of these processes are allowed by Baldwin's rules for ring closure.[26,27] This hypothesis has been confirmed by stopping the reaction (at 3 h) before completion. The alkyne **31** was detected along with traces of the cross-coupling products **23** and **23′**.

The investigation of the competing mechanisms is now ongoing; however, gratifying excellent yields (82−89%) of only the desired six-membered ring were obtained in a stereospecific fashion with copper iodide (Scheme 4).

With the pentacyclic ketones in hand, in excellent yields, the total synthesis of a series of C-19 methyl substituted sarpagine macroline indole alkaloids was undertaken, which included the potent anticancer alkaloid, *N*(4)-methyltalpinine (**10**), as well as the leishmanicidal base (**9**), macrocarpines A-G (**1**-**7**), and, deoxyperaksine (**13**). Herein is reported the first total synthesis of the N_a-H bearing macroline indole alkaloids macrocarpine D (**4**) and E (**5**) (Scheme 6, 7).

Scheme 6. Toward Macrocarpines D (4) and E (5) from the Key Intermediate 17



The pentacyclic ketone (**17**) was subjected to a one-carbon homologation via Wittig olefination using methoxymethyl triphenylphosphonium chloride and potassium *tert*-butoxide in benzene to furnish the enol ether, which was hydrolyzed without purification to aldehyde (**32**) under acidic conditions (Scheme 6). The aldehyde was isolated in the stable α position even in the presence of the C-19 β-methyl group. The aldehyde (**32**) was reduced to alcohol (**33**) with sodium borohydride in ethanol and subsequently protected with a TIPS group to give the silyl ether (**34**). The alkene (**34**) was subjected to hydroboration (borane dimethyl sulfide) and Kabalka oxidation ($NaBO_3$) to provide primary alcohol (**35**) in 73% yield. Oxidation of the primary

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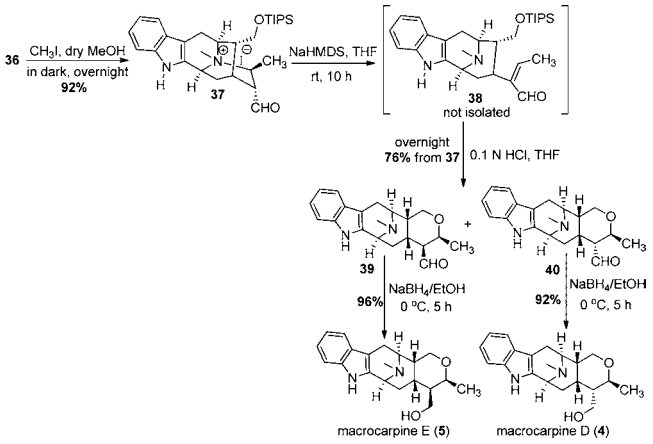
Scheme 7. Total Synthesis of Macrocarpines D (4) and E (5)



alcohol under Corey−Kim conditions at −78 °C produced a mixture of α- and β-aldehydes with the α isomer as the major product. This mixture was epimerized entirely to the α-aldehyde (**36**) with Et_3N in methanol added to the mixture.

Quaternization of the N_b-group with iodomethane in methanol gave the iodide salt (**37**, Scheme 7). The quaternary ammonium salt underwent retro-Michael ring opening in the presence of NaHMDS in THF to produce the α,β-unsaturated aldehyde (**38**) in 78% yield similar to the work first reported by Le Quesne.[5]

The TIPS group was removed by heating **38** under mild acidic conditions in THF. The so-formed alcohol added in Michael fashion to the α,β-unsaturated aldehyde to produce **39** and **40** as an epimeric mixture of aldehydes with the β-methyl group. Each of these could be isolated by silica gel flash chromatography. The desired aldehydes **39** and **40** upon reduction with sodium borohydride in ethanol gave macrocarpine E (**5**) and macrocarpine D (**4**) in 96% and 92% yield, respectively. Spectroscopic data and optical rotations of the synthetic products are in complete agreement with natural macrocarpines D and E. The total synthesis of the other alkaloids of interest is ongoing.

In summary, the first total synthesis of macrocarpines D (**4**) and E (**5**) has been accomplished via a key copper-mediated cross-coupling process toward the important intermediates. This general strategy enables one to access all of the indole alkaloids of the same class with stereospecific incorporation of the important β (or α)-methyl function at C-19. Replacement of the palladium catalyst with CuI provides a much more useful and cheaper method since the copper catalyst, even at stoichiometric amounts, is much cheaper than catalytic palladium (see the SI for a comparative price table). More importantly, accessing **17** in 83% yield with copper compared to 60% with catalytic palladium serves as an example of replacement of palladium in this enolate-mediated process, which makes it much more useful for others, especially in the pharmaceutical industry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01526.

Experimental procedures and spectral data for **17**, **19**, **21**, **23**, and **23′** as well as spectral data and ^1H and ^{13}C comparison tables between natural and synthetic **4** and **5** (PDF)

X-ray crystallographic data for **19** (CIF)

X-ray crystallographic data for **22** (CIF)

X-ray crystallographic data for **23** (CIF)

X-ray crystallographic data for **23′** (CIF)

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Notes

The authors declare no competing financial interest.

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