

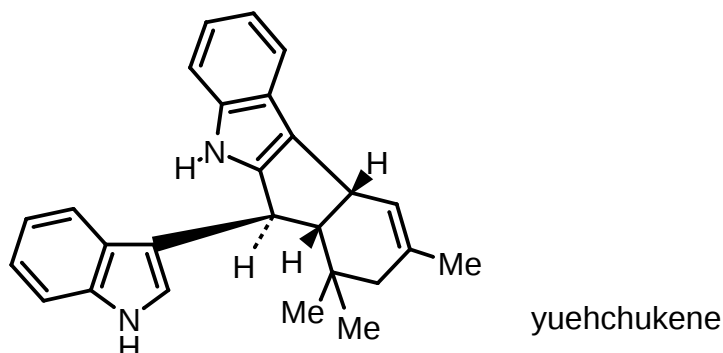
TOTAL SYNTHESIS OF YUEHCHUKENE

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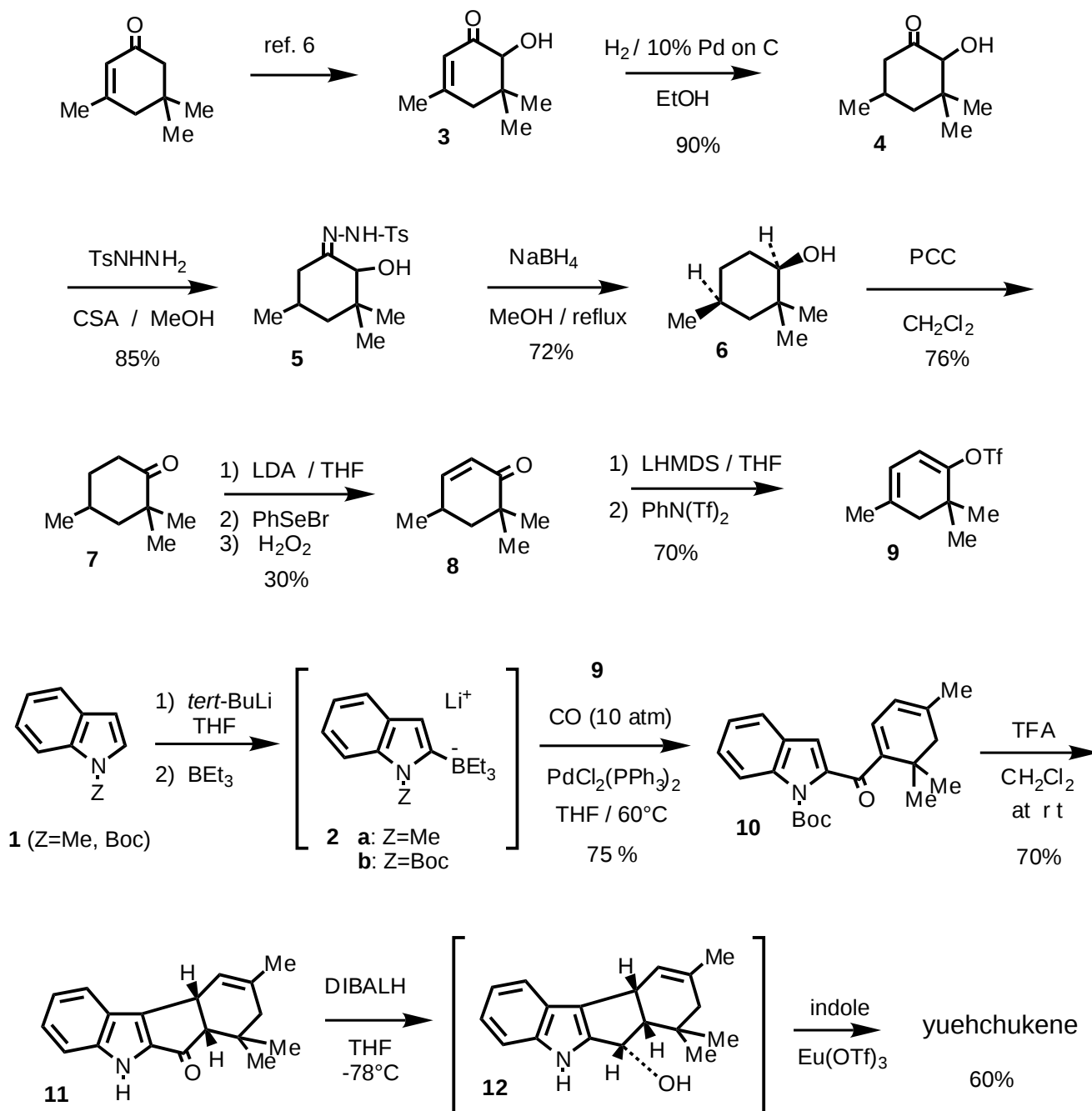
Abstract - Total synthesis of yuehchukene could be realized through the palladium catalyzed carbonylative cross-coupling reaction of indolylborate (**2b**) with cyclohexadienyl triflate (**9**) as a key reaction.

The bis-indole alkaloid, yuehchukene, whose isolation as a racemic mixture from the root bark of *Murraya paniculata* (L.) Jack was reported in 1985,¹ consists of hexahydroindeno[2,1-*b*]indole nucleus. This new class of compound is known to exhibit strong anti-implantation activity and high binding affinity to estradiol receptor, which has been providing several interests in the synthesis of yuehchukene and its analogues,² and in the structure-activity relationships,³ as well. In conjunction with our efforts on the synthetic development of indolylborate,⁴ we have devised a reliable synthesis of yuehchukene derivatives based on the palladium catalyzed carbonylative cross-coupling reaction of indolylborate (**2a**) with cyclohexenyl triflates as a key reaction.⁵ This report describes the total synthesis of yuehchukene based on this protocol.



The requisite cyclohexadienyl triflate (**9**) was prepared according to the sequences in Scheme. Hydroxyisophorone (**3**), readily available from isophorone,⁶ was initially attempted to react with *p*-toluenesulfonyl hydrazide (TsNHNH₂) in MeOH, but this conversion to hydrazone was very sluggish. Thereafter, the reaction of TsNHNH₂ with **4**, obtained by catalytic hydrogenation of **5** on 10% Pd on carbon in EtOH, worked out well, giving hydrazone (**5**) in 85%

yield. Reduction of **5** in MeOH using NaBH₄ afforded alcohol (**6**)⁷ in 72% yield,⁸ and subsequent oxidation of **6** with PCC in CH₂Cl₂ smoothly provided ketone (**7**) in 76% yield. The conversion of **7** to enone (**8**) was effected in 30% yield through phenylselenenylation (LDA / PhSeBr in THF) and oxidation of selenide with H₂O₂ in THF. Treatment of **8** with LHMDS (LiN(TMS)₂) in THF at -30°C, followed by the addition of *N*-phenyltrifluoromethanesulfonimide (PhNTf₂) produced the requisite **9** in 70% yield. The palladium catalyzed carbonylative cross-coupling reaction of indolyborate (**2 b**), generated from indole (**1**: Z=Boc) *in situ*, with **9** was carried out in THF



Scheme

under carbon monoxide atmosphere (10 atm) at 60°C for 20 hours, providing indolylketone (**10**) in 75 % yield. All that remained for realization of the final target was the conversion of **10** to hexahydroindeno[2,1-*b*]indole (**11**) and subsequent introduction of indole to it. Treatment of **10** with TFA in CH₂Cl₂ at room temperature promoted the cyclization, accompanied by the deprotection of *N*-Boc group, to give **11** in 70 % yield. The synthesis of yuehchukene was completed by the reduction of **11** with DIBALH in THF at -78°C to give **12**,⁹ and the subsequent treatment with indole in the presence of Eu(OTf)₃ in THF gave yuehchukene¹⁰ in 60 % yield based on **11**.

In summary, we have developed a useful route to yuehchukene based the palladium catalyzed carbonylative cross-coupling reaction of indolylborate (**2b**) with triflate (**9**).

ACKNOWLEDGEMENTS

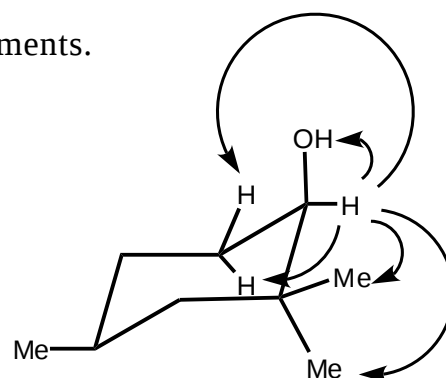
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 7. Structure of **6** was assigned based on NOE experiments.

NOE correlations



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9. Compound (**12**) was used for the next step without purification.
10. Spectral data of yuehchukene: $^1\text{H-NMR}$ (CDCl_3) δ : 0.84 (s, 3H), 1.08 (s, 3H), 1.61 (d, 1H, $J=17$ Hz), 1.65 (s, 3H), 2.25 (d, 1H, $J=17$ Hz), 3.13 (t, 1H, $J=7.8$ Hz), 4.00 (br s, 1H), 4.53 (d, 1H, $J=8.3$ Hz), 5.68 (br s, 1H), 6.96-7.12 (m, 5H), 7.16 (t, 1H, $J=7.3$ Hz), 7.31 (d, 1H, $J=7.8$ Hz), 7.37 (br s, 1H), 7.40 (d, 1H, $J=7.8$ Hz), 7.56 (d, 1H, $J=7.8$ Hz), 7.89 (br s, 1H). $^{13}\text{C-NMR}$ (CDCl_3) δ : 24.1, 28.9, 29.1, 33.5, 37.5, 38.3, 41.0, 60.8, 111.2, 111.7, 118.2, 118.4, 119.3, 119.5, 120.4, 120.5, 122.0, 122.3, 122.9, 124.2, 126.8, 130.2, 136.4, 140.2, 145.2. High-resolution MS m/z : Calcd for $\text{C}_{26}\text{H}_{26}\text{N}_2$: 366.2096. Found: 366.2114.