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TOTAL SYNTHESIS OF YUEHCHUKENE

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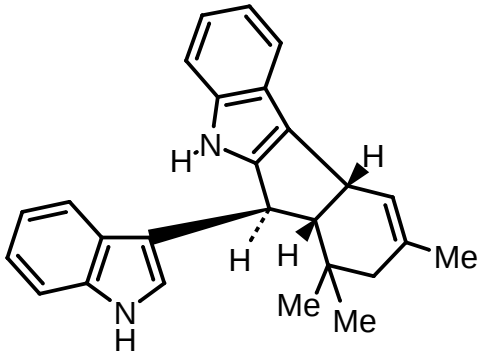
Abstract - Total synthesis of yuehchukene could be realized through the palladium catalyzed carbonylative cross-coupling reaction of indolylborate (**2b**) with cyclohexadienyl triflate (**9**) as a key reaction.

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.

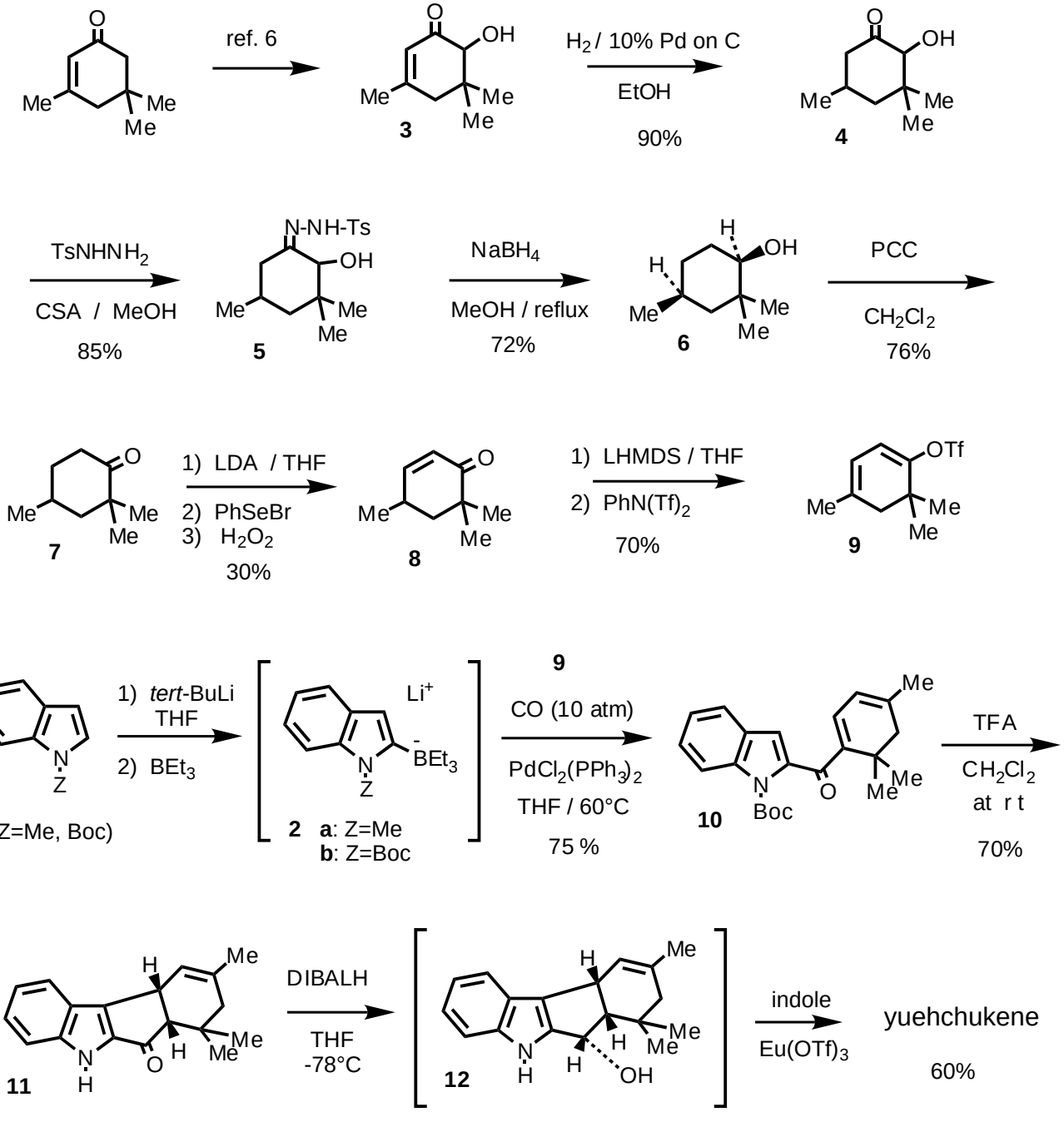


yuehchukene

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 ($TsNHNH_2$) in MeOH, but this conversion to hydrazone was very sluggish. Thereafter, the reaction of $TsNHNH_2$ 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 $NaBH_4$ afforded alcohol (**6**)[7] in 72% yield,[8] and subsequent oxidation of **6** with PCC in CH_2Cl_2 smoothly provided ketone (**7**) in 76% yield. The conversion of **7** to enone (**8**) was effected in 30% yield through phenylselenylation (LDA / PhSeBr in THF) and oxidation of selenide with H_2O_2 in THF. Treatment of **8** with LHMDS ($LiN(TMS)_2$) in THF at -30°C, followed by the addition of *N*-phenyltrifluoromethanesulfonimide ($PhNTf_2$) 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 CH_2Cl_2 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 yuehchukene[10] 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**).

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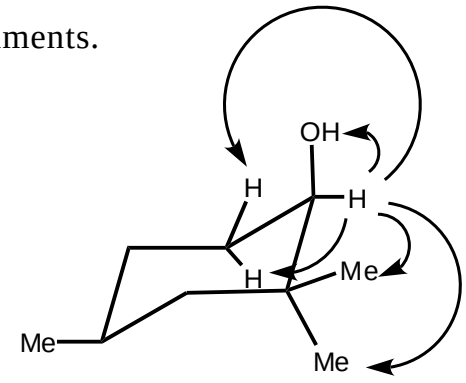
7. Structure of **6** was assigned based on NOE experiments.

NOE correlations



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9. Compound (**12**) was used for the next step without purification.
10. Spectral data of yuehchukene: ^{1}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}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 $C_{26}H_{26}N_2$: 366.2096. Found: 366.2114.