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SYNTHESIS OF (±)-SESBANINE VIA DIRECTED METALATION OF TERTIARY NICOTINAMIDES

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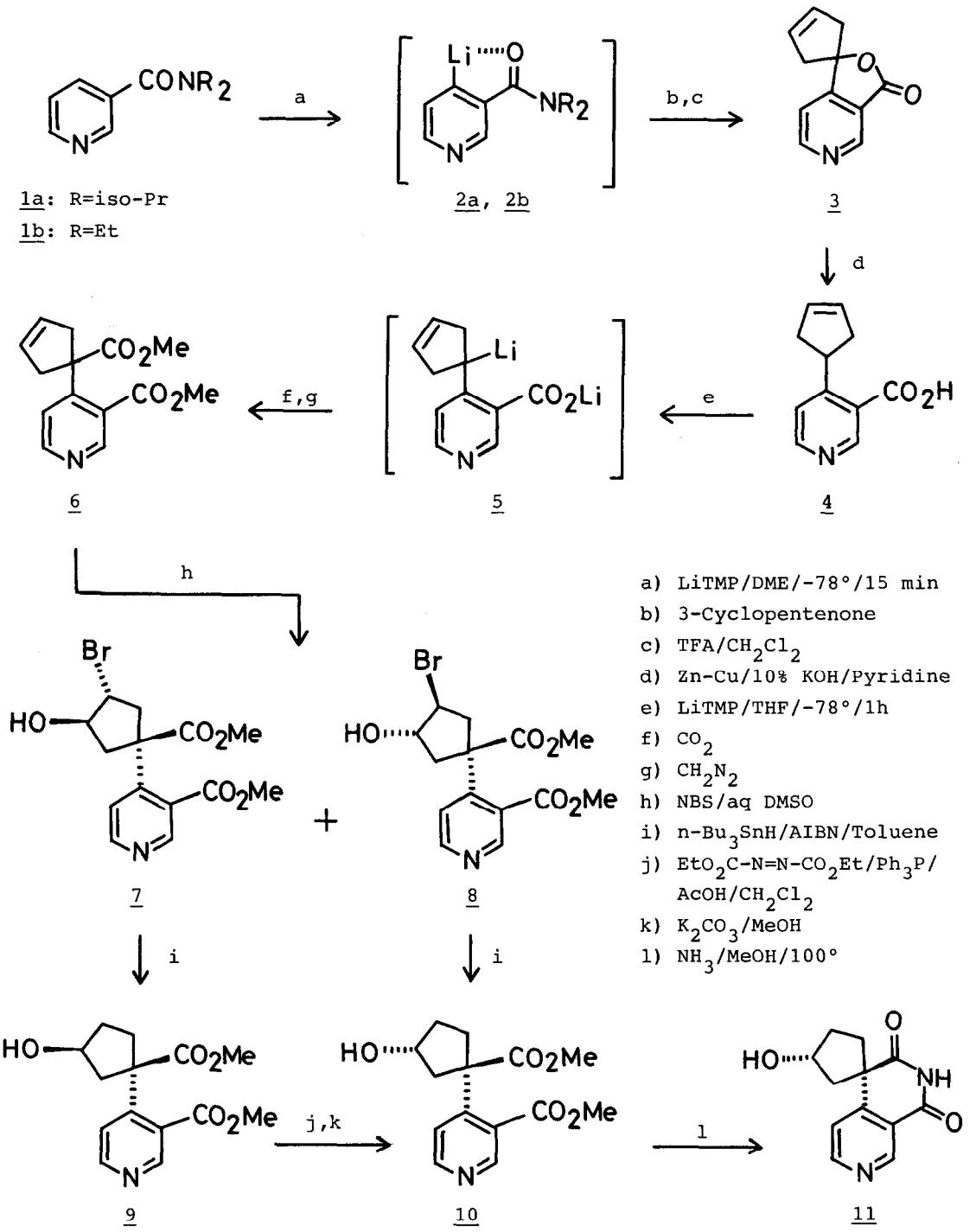
Summary: Racemic sesbanine was synthesized by using regioselective ortho lithiation of N,N-dialkylnicotinamides and subsequent condensation with 3-cyclopentenone as key reactions.

Diverse synthetic utility of tertiary amide-directed metalation of aromatic substrates has been demonstrated by Snieckus and co-workers in the syntheses of highly substituted aromatics, polycyclic aromatic hydrocarbons, condensed heterocycles and a variety of natural products[1]. In this Letter, we report a total synthesis of the cytotoxic alkaloid (±)-sesbanine (11) as a new example of the application of this methodology. This alkaloid was isolated in 1979[2] from ethanolic seeds extracts of Sesbania drumondii which were shown to possess potent antileukemic activity[3]. As a result of its useful activity and previously unknown unique structure, four stereoselective syntheses[4~7] and one chiral synthesis[8] were so far reported.

The starting point of our synthesis was the readily available N,N-diisopropylnicotinamide (1a), which was efficiently and selectively[9] lithiated at the 4-position under the following conditions; 1.2 eq LiTMP/DME/-78°/15 min. Condensation of the lithiated spiecies 2a with 3-cyclopentenone[10] gave the intermediate amide-alcohol, which without isolation, was converted into the spirolactone 3 [11], by treatment with TFA in CH_2Cl_2 at room temperature in 63% overall yield. Although the diethylamide 1b could also be employed as a starting material instead of 1a, the yield of 3 was considerably lower (43%) due to the rapid condensation [12] of the lithiated amide 2b with unreacted 1b under the lithiation conditions. The lactone 3 was reductively cleaved by zinc-copper couple (pyridine/10% KOH/reflux/5 days for 500 mg of 3) to give 4[13] in 94% yield. The acid 4 was again lithiated (2.4 eq LiTMP/THF/-78°/1h) to generate dianion 5 which was carboxylated with dry ice and then, after neutralization by methanolic HCl, treated with a large excess of freshly prepared CH_2N_2, giving the diester 6[14] in 52% overall yield. Treatment of 6 with NBS in aqueous DMSO[15] gave the bromohydrins 7 and 8 in 38% and 21% yields, respectively.


CONR2
a
Li
O
NR2
b,c
O
O
N
1a: R=iso-Pr
1b: R=Et
2a, 2b
3
d
CO2Me
CO2Me
f,g
Li
CO2Li
e
CO2H
6
5
4
h
Br
HO
CO2Me
CO2Me
N
7
8
i
i
HO
CO2Me
CO2Me
j,k
HO
CO2Me
CO2Me
l
HO
O
NH
O
9
10
11
a) LiTMP/DME/-78°/15 min
b) 3-Cyclopentenone
c) TFA/CH2Cl2
d) Zn-Cu/10% KOH/Pyridine
e) LiTMP/THF/-78°/1h
f) CO2
g) CH2N2
h) NBS/aq DMSO
i) n-Bu3SnH/AIBN/Toluene
j) EtO2C-N=N-CO2Et/Ph3P/
AcOH/CH2Cl2
k) K2CO3/MeOH
l) NH3/MeOH/100°

Both bromohydrins were converted into the alcohols 9[16] and 10[17], respectively, on treatment with n-Bu_3SnH/AIBN in warm toluene in excellent yields (9: 96%, 10: 94%). The undesirable alcohol 9 was epimerized into the desirable one 10 by using Mitsunobu's procedure[8,18] (1. 3 eq EtO_2C-N=N-CO_2Et/3 eq Ph_3P/3 eq AcOH /CH_2Cl_2; 2. K_2CO_3/MeOH) in 85% yield. Cyclization of 10 into (±)-sesbanine (11)[19] was accomplished in 80% yield by heating in methanolic NH_3 at 100°. The synthetic alkaloid thus obtained was identical with an authentic specimen.

Moderately good overall yield of 11 (12.5%) from readily accessible amide 2a clearly indicates the usefulness of the directed metalation strategy for the synthesis of (±)-sesbanine. Application of synthon 2 to the preparation of other pyridine alkaloids is in progress in our laboratories.

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11. Compound 3: mp 169-170°(CH_2Cl_2/ether); ir(Nujol): 1760 cm^{-1}; nmr($CDCl_3$): δ 2.94(s, 4H), 5.83(s, 2H), 7.43(d, 1H, J=5.5 Hz), 8.77(d, 1H, J=5.5 Hz), 9.03(s, 1H); Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48; Found: C, 70.69; H, 4.85; N, 7.52.
12. N,N-Diehtyl-4-nicotinoylnicotinamide was isolated.

13. Compound 4: mp 165-166°(dec)(AcOEt); ir(Nujol): 1710 cm^{-1}; nmr($CDCl_3$): δ 2.1-3.3(m, 4H), 4.6(br s, 1H), 5.77(s, 2H), 7.45(d, 1H, J=5.5 Hz), 8.67 (d, 1H, J=5.5 Hz), 9.13(s, 1H), 13.20(s, 1H); Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40; Found: C, 69.34; H, 5.92; N, 7.46. This acid was very soluble in water. Pure material could be isolated from inorganic salts by using ion-exchange resin (Dowex-50, H^+-form, elution with 2M aqueous pyridine).
14. Compound 6: mp 40.5-41°(ether/hexane); ir(Nujol): 1730 cm^{-1}; nmr($CDCl_3$): δ 2.77(d, 2H, J=16 Hz), 3.31(d, 2H, J=16 Hz), 3.63(s, 3H), 3.84(s, 3H), 5.68 (s, 2H), 7.20(d, 1H, J=5.5 Hz), 8.58(d, 1H, J=5.5 Hz), 8.96(s, 1H); Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36; Found: C, 64.26; H, 5.81; N, 5.33.
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16. Compound 9: mp 73.5-75°(ether/hexane); nmr($CDCl_3$): δ 1.7-2.9(m, 6H), 3.63 (s, 3H), 3.87(s, 3H), 4.36(br s, 1H), 7.31(d, 1H, J=5.5 Hz), 8.64(d, 1H, J=5.5 Hz), 8.94(s, 1H); Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02; Found: C, 60.07; H, 6.12; N, 5.01.
17. Compound 10: mp 130.5-131°(CH_2Cl_2/ether); nmr($CDCl_3$): δ 1.7-3.1(m, 6H), 3.58(s, 3H), 3.84(s, 3H), 4.53(br s, 1H), 7.53(d, 1H, J=5.5 Hz), 8.57(d, 1H, J=5.5 Hz), 8.84(s, 1H); Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.14; N, 5.02; Found: C, 60.12; H, 6.19; N, 5.14.
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19. Compound 11: mp 239-241.5°(MeOH/AcOEt); ms: m/e=232(M^+); ir(Nujol): 3510, 1710(sh), 1690, 1597 cm^{-1}; nmr(DMSO-d_6): δ 1.7-2.4(m, 5H), 2.67(dd, 1H, J=14.5 and 5.5 Hz), 4.50(br s, 1H), 5.00(br s, 1H), 7.88(d, 1H, J=5.5 Hz), 8.80(d, 1H, J=5.5 Hz), 9.06(s, 1H), 11.2(br s, 1H).

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