Tetrahedron Letters, Vol.31, No.8, pp 1081-1084, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

A REGIOSELECTIVE DIELS-ALDER SYNTHESIS OF ELLIPTICINE[1]

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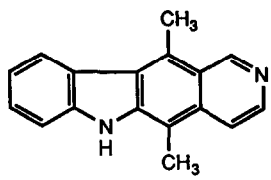
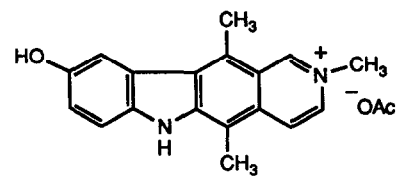
Summary: *The trimethylsilyl trifluoromethanesulfonate accelerated Diels-Alder reaction between 1,3-dimethyl-4-(phenylsulfonyl)-4H-furo[3,4-b]indole (**3**) and 5,6-dihydropyridones (**10**) shows high regioselectivity, yielding carbazole **11** upon hydrolytic workup. Carbazole **11b** has been successfully converted to the pyridocarbazole alkaloid ellipticine (**1**).*

The pyrido[4,3-*b*]carbazole alkaloid ellipticine (**1**) exhibits pronounced anticancer activity in several animal and human systems[2] and a derivative, 2-methyl-9-hydroxyellipticinium acetate ("elliptinium", **2**), is a clinically proven drug for the treatment of metastatic breast cancer, myeloblastic leukemia, and some solid tumors.[3] Because of its great biological activity, ellipticine has been the target of many synthetic endeavors.[4]

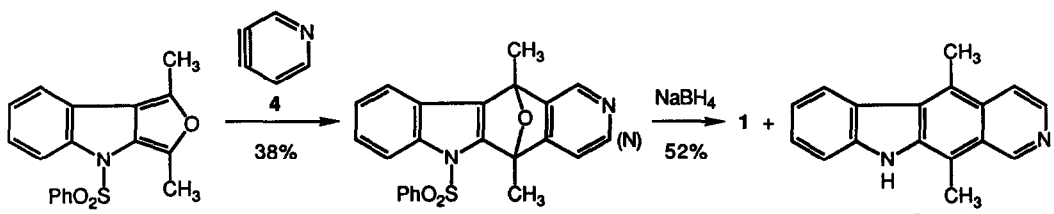


1

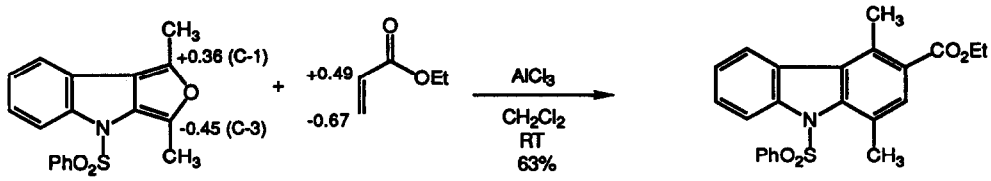


2

In 1984, we reported a novel synthesis of ellipticine via a Diels-Alder reaction between 1,3-dimethyl-4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole (**3**) and 3,4-pyridyne (**4**).[5] Unfortunately, this reaction showed little or no regioselectivity and thus "isoellipticine" (**5**) was also a major product. Moody has also shown that pyridyne **4** undergoes a nonregioselective cycloaddition reaction with 1,4-dimethylpyrano[3,4-*b*]indole, producing a 1:1 mixture of **1** and **5** in 40% combined yield.[6]



This lack of regioselectivity apparently is due to the high reactivity of **4**. MINDO 3 calculations performed on **3** reveal in the HOMO a large positive coefficient at C-1 and a large negative coefficient at C-3.[7] Matching these coefficients with those for the LUMO of acrylates[8] predicts a strong regiochemical bias in the Diels-Alder reaction. This prediction has in fact been substantiated. Thus, in unpublished work, we have found that the aluminum chloride promoted reaction between **3** and ethyl acrylate yields only **6**, with no trace of the regioisomeric product.[7]

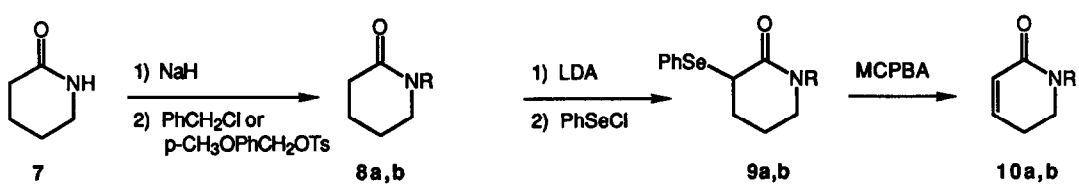


3
HOMO

LUMO

6

We therefore reasoned that a dienophile such as 5,6-dihydropyridone **10** would exhibit better regiocontrol in the Diels-Alder reaction and would serve as a synthetic equivalent for 3,4-pyridyne (**4**). **10a** was readily prepared in three steps from commercially available δ-valerolactam (**7**). Thus, **7** was treated sequentially with sodium hydride and benzyl bromide in dimethylformamide (DMF) to yield the known[9] lactam **8a** (85%). Using the methodology of Zoretic,[10] we lithiated **8a** with lithium diisopropylamide (LDA) and quenched with phenylselenenyl chloride to yield **9a** in 53% yield after chromatography. Oxidative elimination of the phenylselenide was accomplished in 61% yield by treatment of **9a** with m-chloroperoxybenzoic acid (MCPBA) to give **10a**.[11]



7

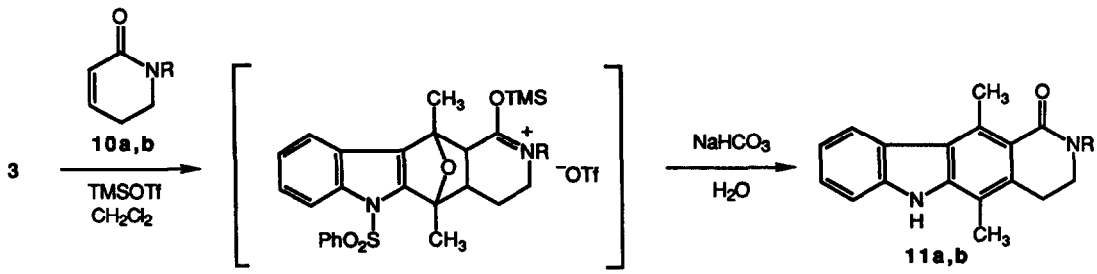
8a,b

9a,b

10a,b

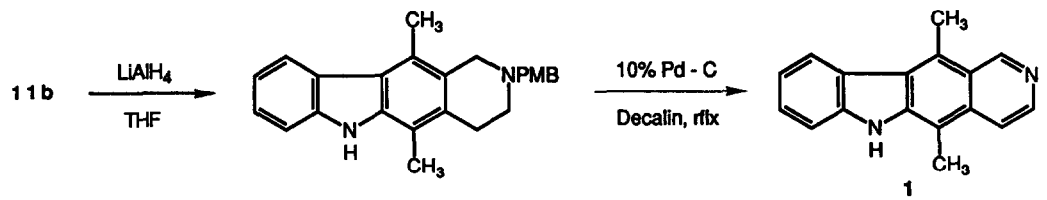
(**a**, R = $PhCH_2$; **b**, R = *p*-CH_3OPhCH_2 (PMB))

With the diene and dienophile in hand, the stage was set for the Diels-Alder reaction. Initial attempts to accomplish this cycloaddition gave no reaction at room temperature and decomposition of **10a** at elevated temperatures. The use of Lewis acid promoters such as $AlCl_3$, BF_3-Et_2O, $TiCl_4$, $SnCl_4$, $EtAlCl_2$, Et_2AlCl, and $ZnCl_2$ also resulted in the decomposition of **10a**. Ultimately, the Diels-Alder reaction was accomplished using trimethylsilyl trifluoromethanesulfonate (TMSOTf) activation, as recently described by Jung,[12] to give after basic workup, **11a** as the sole product in 76% yield.[13] Unfortunately, conversion of **11a** to ellipticine has not yet been accomplished as removal of the benzyl group has proved to be more difficult than we had anticipated.



(**a**, R = $PhCH_2$; **b**, R = *p*-CH_3OPhCH_2)

To circumvent this difficulty, we turned our attention to a different nitrogen protecting group. Thus, 1-(p-methoxybenzyl)-5,6-dihydropyridone (**10b**) was prepared from δ-valerolactam analogously to **10a** by treatment with NaH and p-methoxybenzyl tosylate (PMBOTs, prepared in situ from p-methoxybenzyl alcohol, NaH, and p-toluenesulfonyl chloride in ether at -78°C) to give **8b** in 68%. Lithiation with LDA, addition of phenylselenenyl chloride (94%) and oxidative elimination (MCPBA, 78%) gave the desired lactam **10b**.[11]



The TMSOTf accelerated Diels-Alder reaction between dienophile **10b** and **3** was successful, giving **11b** regioselectively in a more modest 40% yield.[13] The low yield is presumably due to the decomposition of the lactam as a result of deprotection during the reaction. Nevertheless, **11b** was converted to ellipticine (**1**) in two steps by first reducing the carbonyl with lithium aluminum hydride and then effecting aromatization and concomitant debenzylation (10% Pd/C, decalin, reflux, 24 hours) to give ellipticine (20% yield, two steps). Comparison of this product with authentic samples of ellipticine and isoellipticine (**5**) by TLC and UV showed unequivocally that the product was >99% ellipticine, as none of the isomeric isoellipticine (**5**) could be detected by TLC under conditions that would have revealed as little as 1% contamination by **5**. Thus, although the yield of ellipticine remains to be improved, we have demonstrated that a Diels-Alder cycloaddition strategy is feasible for the synthesis of this ring system.

Acknowledgements: This investigation was supported by PHS Grant GM-30761 awarded by the National Institutes of Health, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and Merck Sharp and Dohme Research Laboratories. We also thank the National Science Foundation for funds to purchase a Varian XL-300 NMR spectrometer.

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11. **10a:** Bp 115-120 °C/0.2 torr; IR (neat) 3040, 2980, 2840, 1660, 1610, 1260, 1070, 1020, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (s, 5H), 6.55-6.49 (m, 1H), 5.97-5.93 (m, 1H), 4.60 (s, 2H), 3.32-3.18 (m, 2H), 2.32-2.18 (m, 2H); MS 187 (M^+, 100%), 132, 110, 96, 91, 77.
10b: Bp 180-185 °C/1.0 torr; mp 45-46 °C; IR ($CHCl_3$) 3000, 2940, 2830, 1660, 1605, 1505, 1235, 1210 cm^{-1}; NMR ($CDCl_3$) δ 7.17-7.12 (m, 2H), 6.80-6.78 (m, 2H), 6.50-6.45 (m, 1H), 5.93-5.89 (m,1H), 4.47 (s, 2H), 3.71 (s, 3H), 3.29-3.15 (m, 2H), 2.30-2.16 (m, 2H); MS 217 (M^+, 100%), 202, 186, 121, 96.
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13. **11a:** Mp 179-180 °C (dec.); IR ($CHCl_3$) 3500, 3080, 3050, 2980, 2940, 2880, 1630, 1600, 1590, 1550, 1350, 1340, 1250 cm^{-1}; NMR ($CDCl_3$) δ 10.52 (s, 1H), 8.30-8.25 (m, 1H), 7.54-7.10 (m, 8H), 4.85 (s, 2H), 3.50-3.42 (m, 2H), 3.25 (s, 3H), 2.92-2.82 (m, 2H), 2.36 (s, 3H); MS 354 (M^+), 263, 235, 207, 91 44 (100%); UV (95% EtOH) 210, 242, 250, 270, 282.
11b: Mp 235-236 °C (dec.); IR ($CHCl_3$) 3660, 3020, 2950, 2850, 1640, 1600, 1510, 1420, 1390, 1325, 1240, 1045, 820 cm^{-1}; NMR ($CDCl_3$) δ 10.79 (s, 1H), 8.17 (d, 1H, J=7.9 Hz), 7.48-7.46 (m, 1H), 7.33-7.28 (m, 1H), 7.24-7.21 (m, 2H), 7.15-7.10 (m, 1H), 6.80-6.77 (m, 2H), 4.68 (s, 2H), 3.71 (s, 3H), 3.41-3.37 (m, 2H), 3.16 (s, 3H), 2.88-2.84 (m, 2H), 2.39 (s, 3H); MS 384 (M^+, 100%) 369, 276, 263, 235, 207, 192, 121, 91, 77; UV (95% EtOH) 210, 240, 250, 270, 282.

(Received in USA 22 November 1989)