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AN EFFICIENT ENANTIOSELECTIVE SYNTHESIS OF (+)-INDICINE N-OXIDE, AN ANTITUMOR PYRROLIZIDINE ALKALOID

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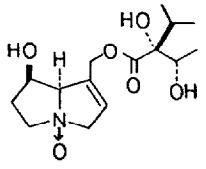
Summary: An antitumor pyrrolizidine alkaloid, (+)-indicine N-oxide (**1**) has been synthesized enantioselectively in five steps starting with a lactone **4**.

Indicine N-oxide (**1**) is the major alkaloid of the plant Heliotropium indicum[1] and is known to be the only pyrrolizidine alkaloid which has undergone clinical trials as an anticancer drug.[2] Although several synthetic routes to indicine N-oxide (**1**) have been reported recently,[3] there seems to be little progress on the enantioselective synthesis of this chemotherapeutically interesting alkaloid. Described herein is an efficient synthesis of the natural enantiomer of indicine N-oxide (**1**).

The present synthesis of (+)-indicine N-oxide (**1**) requires (+)-retronecine (**2**) and an optically active protected necic acid **3a** or **3b**. We have already achieved enantioselective synthesis of (+)-**2**.[4] Our effort was therefore concentrated on the preparation of **3a** or **3b** starting with readily accessible (2S,5S)-2-(t-butyl)-5-isopropyl-1,3-dioxolan-4-one (**4**).[5] Homochiral lactone **4**[6] was converted into the corresponding enolate by reaction with LDA (1.5 equiv) in THF at -100 °C for 1 h.[7] Subsequent reaction of the enolate with acetaldehyde (2.3 equiv) at -100 °C provided the desired lactone alcohol **5**[8] [colorless oil, $[\alpha]_D^{16}$ +2.24° (c 0.98, $CHCl_3$), 43%] and the diastereomer **6** [mp 108-109 °C (pentane), 5%] after separation by HPLC. Of the possible four diastereomers, the desired **5** was obtained preferentially by this procedure. The stereochemistry of **5** and **6** was established unambiguously by their



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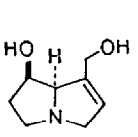

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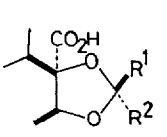
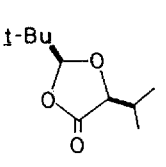


3a R^1 = t-Bu, R^2 = H
3b R^1 = H, R^2 = t-Bu



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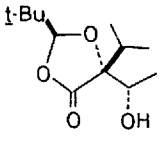

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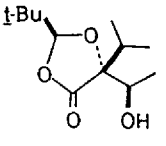

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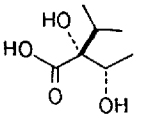

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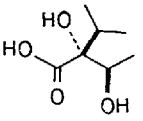

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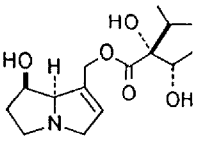

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transformation into (-)-trachelanthic acid (**7**)[9a] and (+)-viridifloric acid (**8**),[9b] respectively by acidic hydrolysis (1 M HCl, reflux, 3 h). Lactone alcohol **5** was subjected to acid-catalyzed isomerization (camphorsulfonic acid, benzene, reflux, 3 days) to furnish the protected necic acids **3a** [mp 107-108.5 °C (pentane), $[\alpha]_D^{14}$ +13.6° (c 1.02, $CHCl_3$), 77%] and **3b** [mp 66.5-68 °C (pentane), $[\alpha]_D^{14}$ +13.5° (c 0.85, $CHCl_3$), 12%].[10]

For the synthesis of (+)-indicine N-oxide (**1**), (+)-retronecine (**2**) was coupled with each of the protected necic acids **3a** and **3b** . Thus, treatment of (+)-**2** and **3a** (1 equiv) with DCC (2.3 equiv) and DMAP (0.3 equiv) (toluene, room temp., 6 days) gave protected indicine, which upon hydrolysis (1 M HCl, room temp., 22 h) provided (+)-indicine (**9**) [colorless oil, $[\alpha]_D^{18}$ +20° (c 0.40, EtOH), 75% overall]. Similarly, (+)-**9** was also obtained in 63% from (+)-**2** and **3b**. Finally, oxidation of (+)-**9** with m-CPBA (acetone, room temp., 2 h) furnished (+)-indicine N-oxide (**1**) [mp 119-120 °C (MeOH-acetone), $[\alpha]_D^{19}$ +35.6° (c 0.85, EtOH), 81%]. Spectral and physical properties of synthetic **1** were identical with those of natural **1** in all respects.[11] In conclusion, the natural enantiomer of indicine N-oxide (**1**) was synthesized from lactone **4** in five steps and in 20% overall yield.

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References and Notes.

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6. The compound **4** reported in the literature[5] contained a small amount (2.5%) of the 2R-isomer of **4**. We could prepare pure **4** by recrystallization of the crude **4** at -78 °C. Pure **4**: >99% ee by ^1H NMR shift analysis using Eu(hfc)$_3$, $[\alpha]_D^{24}$ -1.66° (c 3.07, $CHCl_3$), bp 104 °C (21 mmHg).
7. When the enolate formation and subsequent addition reaction were conducted at -78 °C, a 5:3 mixture of **5** and **6** was obtained in 38% yield. The lower yield of **5** and **6** was due to the decomposition of a considerable amount of the lactone enolate into the ketene during the enolate formation at -78 °C.
8. All new compounds exhibited satisfactory spectral (^1H NMR, IR, and MS) and analytical data. All yields refer to materials purified by HPLC on ODS or column chromatography on silica gel.
9. a) Synthetic **7**: mp 88.5-89.5 °C (benzene-hexane), $[\alpha]_D^{14}$ -4.46° (c 1.01, EtOH); lit.[3d] mp 89.5-90 °C (benzene-hexane), $[\alpha]_D^{25}$ -4.8° (c 0.51, EtOH).
b) Synthetic **8**: mp 117-118 °C (hexane-ether), $[\alpha]_D^{19}$ +1.92° (c 0.73, H_2O); lit.[3c] mp 119 °C, $[\alpha]_D^{25}$ +2.8° (c 1.00, H_2O).
10. The stereochemistry of **3a** and **3b** was determined by the NOE experiments.
11. Natural indicine N-oxide: mp 119-120 °C (EtOAc-i-PrOH), $[\alpha]_D$ +34.8° (c 1.00, EtOH);[1b] mp 119-120 °C (MeOH-acetone), $[\alpha]_D^{21}$ +34.8° (EtOH).[3d]

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