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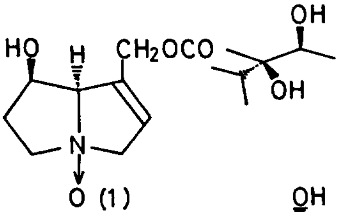
THE TOTAL SYNTHESES OF (-)-INDICINE N-OXIDE AND INTERMEDINE N-OXIDE

Yoshio Nishimura,* Shinichi Kondo and Hamao Umezawa
Institute of Microbial Chemistry
3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141.

Abstract: The total syntheses of (-)-indicine N-oxide, the enantiomer of natural indicine N-oxide and intermedine N-oxide have been achieved.

Indicine-N-oxide (1)[1] is the first pyrrolizidine alkaloid to be selected for clinical trials against cancer, while heliotridine (2)[2] is an established carcinogen. The monoester pyrrolizidine alkaloids containing $\Delta^{1,2}$-unsaturated dihydroxynecine base such as retronecine and heliotrine have been attractive synthetic targets because of their intriguing chemical structures as well as their interesting and diverse pharmacological activities.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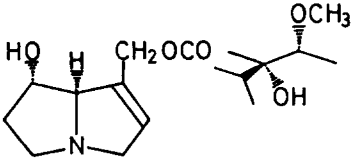
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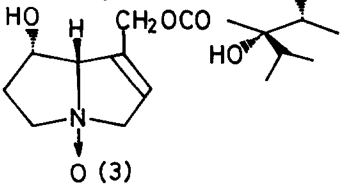
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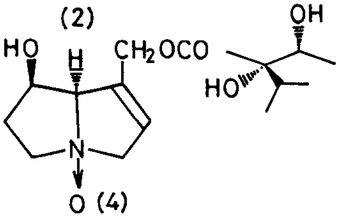
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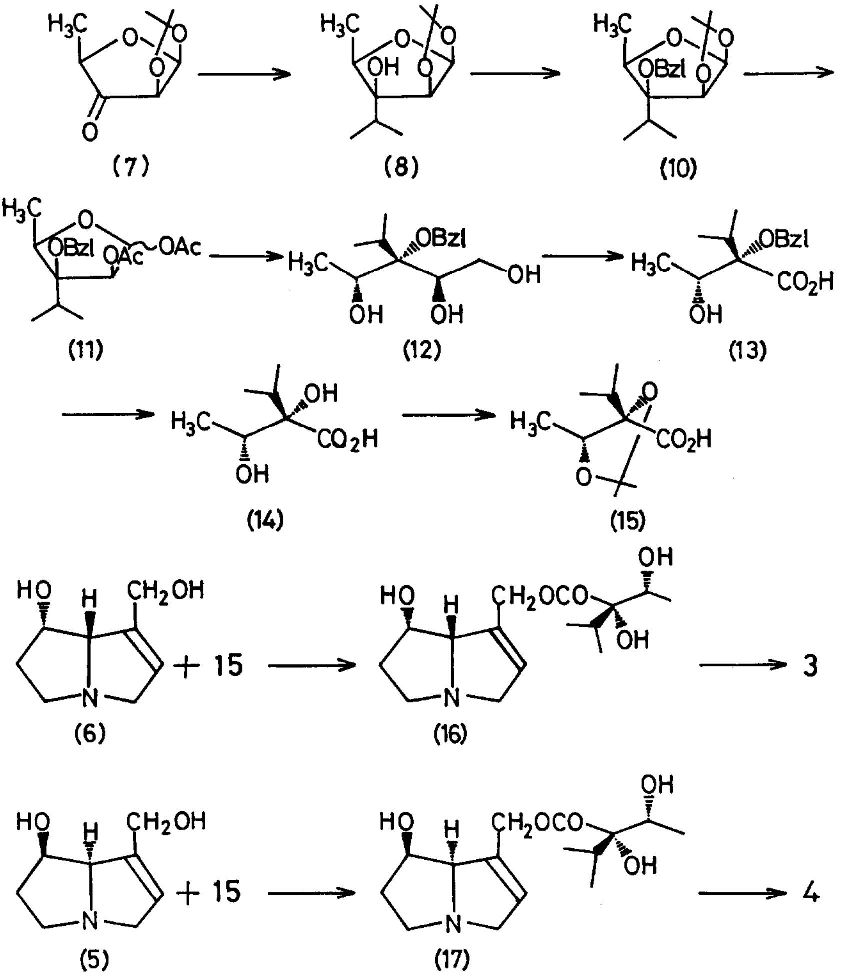
Here we wish to report the total syntheses of (-)-indicine N-oxide (3), the enantiomer of natural indicine N-oxide and intermedine N-oxide (4). The syntheses of 3 and 4 have been achieved in a totally stereospecific fashion through the following sequence as the key steps: (a) the enantioselective synthesis of retronecine (5) and its enantiomer (6), (b) the enantioselective synthesis of (+)-trachelanthic acid (**14**), and (c) a combination of each segments. In previous paper[3] we have already reported the syntheses of **5** and **6** by a convergent method employing D-glucose as a chiral source. In this paper we describe the first enantioselective synthesis of **14**[4] and the coupling of **5** and **6** with protected (+)-trachelanthic acid (**15**) followed by oxidation, to form **3** and **4**.

Grignard reaction of 1,2-O-isopropylidene-5-deoxy-β-D-threo-pentofuranos-3-ulose (**7**)[5] with 3 equiv of isopropylmagnesium bromide [$(CH_3)_2CHMgBr$, ether, -78°C → RT] occurred stereospecifically to afford 1,2-O-isopropylidene-5-deoxy-3-C-isopropyl-β-D-lyxofuranose (**8**)[6] [52%, mp 37.5-38.5°C, $[\alpha]_D^{20}$ +9.8° ($CHCl_3$)] and 1,2-O-isopropylidine-5-deoxy-β-D-lyxofuranose (**9**) (35%). The configuration of branched-chain at C-3 is assigned on the observation of NOE between 3-C-isopropyl and the protons at C-2 and C-4, and between 3-OH and the methyl groups of 1,2-O-isopropylidene and C-4. This is also confirmed by successful transformation to natural (+)-trachelanthic acid (**14**). Swern oxidation[7] of by-product **9** [$(COCl)_2$, DMSO, CH_2Cl_2] was effectively recycled to **7**. Benzylation of tertiary alcohol of **8** (benzyl chloride, NaH, DMF, 0°C → RT) gave a corresponding benzyl ether **10** [94%, oil, $[\alpha]_D^{25}$ +15.9° ($CHCl_3$)]. Hydrolysis of **10** by treatment with a mixture of 70% acetic acid and 6 M hydrochloric acid followed by acetylation (Ac_2O, pyridine) produced α-acetate of **11** [84%, oil, $[\alpha]_D^{27}$ +62.7° ($CHCl_3$)] and β-acetate of **11** [6%, oil, $[\alpha]_D^{27}$ +3.9° ($CHCl_3$)]. Borohydride reduction of **11** (20 equiv $NaBH_4$, EtOH, reflux) afforded the tetraol **12** [72%, oil, $[\alpha]_D^{25}$ +6.8° ($CHCl_3$)]. Lemieux-von Rudloff oxidation[8] of **12** (4 equiv $NaIO_4$, 0.4 equiv $KMnO_4$, Na_2CO_3, t-BuOH-H_2O) yielded the carboxylic acid **13** [81%, oil, $[\alpha]_D^{25}$ -16.5° ($CHCl_3$)]. Removal of protected group of **13** by hydrogenolysis (10% Pd-C, H_2 gas, MeOH) afforded (+)-trachelanthic acid (**14**)[6] [90%, mp 89.5-90°C, $[\alpha]_D^{25}$ +4.0° (EtOH) (lit,[4c] mp 89-90°C and $[\alpha]_D^{25}$ +3.8° (H_2O)], whose structure was also supported by ^1H NMR and ^{13}C NMR spectra. The resulting acid **14** was converted to the acetonide **15**[6] by treatment of 20 equiv of 2,2-dimethoxypropane and a trace amount of conc. hydrochloric acid [90%, mp 54.5-55.5°C, $[\alpha]_D^{25}$ -34.2° (EtOH) (lit,[9] (-)-trachelanthic acid acetonide: mp 51-53°C and $[\alpha]_D^{25}$ +35.9±0.5° (EtOH)].

For the synthesis of (-)-indicine N-oxide (**3**), the coupling of **6** and **15** was accomplished by the recently reported mild esterification method.[9,10] Treatment of **6** and **15** with N,N'-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) in toluene followed by hydrolysis with 0.6 M hydrochloric acid afforded (-)-indicine (**16**) [71%, foam, $[\alpha]_D^{22}$ -19° (EtOH) (indicine[11]: $[\alpha]_D^{22}$ +20° (EtOH)], identical in all respects with natural indicine[12] except for the sign of the specific rotation. Oxidation of **16** with m-chloroperbenzoic acid (mCPBA) in dry acetone gave **3** [84%, mp 119-121°C, $[\alpha]_D^{21}$ -34.7° (EtOH) (lit,[1a] indicine N-oxide: mp 119-120°C and $[\alpha]_D^{21}$ +34.8° (EtOH)]. Its spectral properties (IR, ^1H NMR, ^{13}C NMR and mass spectra) were superimposable with those of natural indicine N-oxide.[12]

The synthesis of intermedine N-oxide (**4**) was achieved through the same sequence used for the synthesis of (-)-indicine N-oxide. Esterification of **5** with **15** (DCC, DMAP, toluene) followed by acid hydrolysis (0.6 M hydrochloric acid) produced intermedine (**17**) [76%, mp 140-141°C, [α]$_D^{23}$ +6.3° (EtOH) (lit,[13,14] mp 141-142°C, [α]$_D^{20}$ +4.8° (EtOH), +9.8° (EtOH)], identical in all respects with natural intermedine.[15] Oxidation of **17** with mCPBA in dry acetone afforded **4** [98%, hygroscopic solid, [α]$_D^{20}$ +8.6° (EtOH)]. The structure of **4** was confirmed by ^{1}H NMR, ^{13}C NMR, IR and mass spectra.



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6. 8: ^{1}H NMR (400 MHz, $CDCl_3$) δ0.96 (6H d, J=6.7 Hz, CH_3 of 3-C-isopropyl), 1.31 (3H d, J=6.7 Hz, 4-CH_3), 1.40 and 1.62 (3H each s, isopropylidene), 1.77 (1H heptet, J=6.7 Hz, CH of 3-C-isopropyl), 2.92 (1H s, 3-OH), 4.08 (1H q, J=6.7 Hz, H-4), 4.32 (1H d, J=4.0 Hz, H-2) and 5.65 (1H d, J=4.0, H-1). 14: ^{1}H NMR (400 MHz, $CDCl_3$) δ0.96 and 0.99 (3H each d, J=7 Hz, CH_3 of isopropyl), 1.26 (3H d, J=6.5 Hz, CH_3), 2.01 (1H heptet, J=7 Hz, CH of isopropyl) and 2.24 (1H q, J=6.5 Hz, H-3). 15: ^{1}H NMR (400 MHz, $CDCl_3$) δ0.91 and 1.02 (3H each d, J=6.7 Hz, CH_3 of isopropyl), 1.50 (3H d, J=6.5 Hz, CH_3), 2.20 (1H heptet, J=6.7 Hz, CH of isopropyl) and 4.36 (1H q, J=6.5 Hz, H-3).
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