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Total Syntheses of Indicine *N*-Oxide, Intermedine *N*-Oxide, and Their Enantiomers Using Carbohydrate as a Chiral Educt

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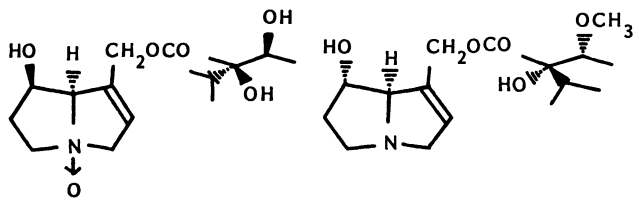
The first completely enantioselective syntheses of indicine *N*-oxide, intermedine *N*-oxide, and their enantiomers have been achieved stereospecifically. A synthetic analogue modeled on indicine *N*-oxide showed the superior activity to indicine *N*-oxide itself against cancer cell in vitro test.

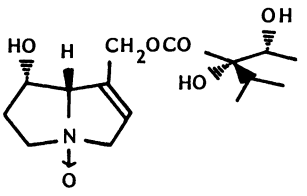
The pyrrolizidine alkaloids constitute an exceptionally large class of naturally occurring materials which possess in common the 1-azabicyclo[3.3.0]-octane skelton often functionalized by hydroxyl or stereochemically complex carboxylic ester moieties at a variety of structural sites. The pyrrolizidine alkaloids containing $\Delta^{1,2}$-unsaturated subgroup are associated with wide range of potent biological effects.[1] Indicine *N*-oxide (**1**)[2] shows marked antitumor effects without the hepatotoxicity normally associated with this class of compounds, while the very similar heliotrine (**2**)[1a,3] is an established carcinogen. Due to their intriguing chemical structures and their pharmacological activities, the $\Delta^{1,2}$-unsaturated pyrrolizidine alkaloids have attracted the synthetic attention in recent years.[4]

In order to investigate the relationships between structure and antitumor activity, we undertook the syntheses of **1** and three possible diastereomer (**3**—**5**)[5] of **1** by coupling of (+) and (−)-retronecine (**18** and **19**) with (+) and (−)-trachelanthic acid (**13** and **16**). Although the formal and relay syntheses of indicine (**23**)[6] and intermedine (**21**),[6,7] and the synthesis of inseparable four diastereomeric mixture of **22** by the combination of racemic retronecine and racemic trachelanthic acid[8] have been reported, little is known about the completely enantioselective syntheses of **21**, **22** and their enantiomers. Recently, we succeeded in the enantioselective synthesis of retronecine and its enantiomer.[9] In this paper we wish to report the first enantioselective syntheses of **1**, **3**, **4**, and **5** in a totally stereospecific fashion via the enantioselective synthesis of (+) and (−)-trachelanthic acid. Compounds **1** and **4** are enantiomers of compounds **3** and **5**, respectively. Here we also wish to present the synthesis of active analogue **26** of **1** against cancer cells in vitro test by the regioselective esterification of retronecine with (*S*)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (**24**).

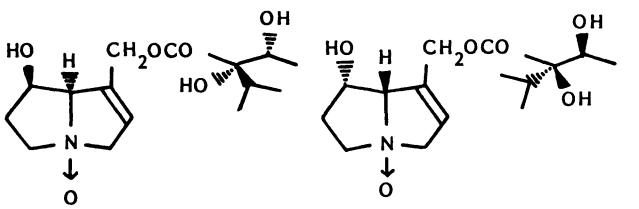


1: Indicine N-oxide 2: Heliotrine

Fig. 1.



3: (-)-Indicine N-oxide



4: Intermedine N-oxide 5: (-)-Intermedine N-oxide

Fig. 2.

Results and Discussion

Synthesis of (+) and (−)-Trachelanthic Acid. The hitherto-known syntheses of trachelanthic acid are all of racemic form,[10] and **13** and **16** have been prepared via its optical resolution. Our approach to **13** and **16** involves, as the key step, the synthesis of a specific branched-chain sugar having a hydroxyl group and a isopropyl group at the branched position. Recently, a route to a branched-chain sugar having such asymmetric center by several steps have been described by Redlich.[11] The simple construction of such asymmetric center by one step sequence has been examined by Grignard reaction using isopropyl-magnesium halide with a ulose having the desired stereochemistry.

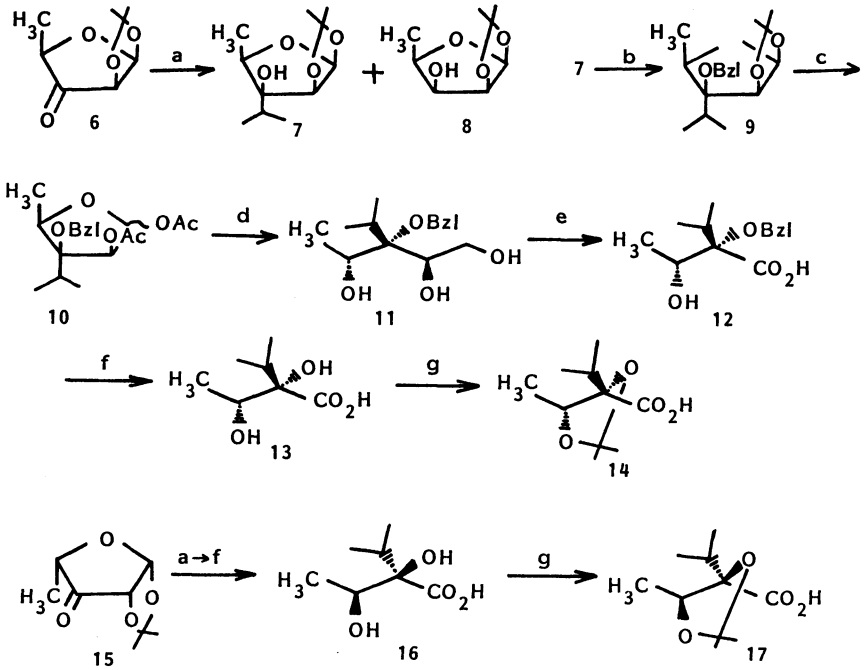
Grignard reaction of **6** with 3 equiv of isopropyl-magnesium bromide occurred stereospecifically to afford 1,2-*O*-isopropylidene-5-deoxy-3-*C*-isopropyl-β-D-lyxofuranose (**7**) and 1,2-*O*-isopropylidene-5-deoxy-β-D-lyxofuranose (**8**) in a yield of 52 and 35%, respectively. Stereospecific addition and reduction were caused by the attack of the bulky Grignard reagent to the carbonyl group from less sterically

hindered side. 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 (**13**). Swern oxidation[12] of by-product **8** was effectively recycled to **6**. Benzylation of tertiary alcohol of **7** gave a corresponding benzyl ether **9** in a yield of 94%. Acid hydrolysis of **9** followed by acetylation produced an anomeric mixture **10** (α: 84%, β: 6% yield). Borohydride reduction of **10** afforded the tetrol **11** in a yield of 72%. Lemieux-von Rudloff oxidation[13] of **11** yielded the carboxylic acid **12** in a yield of 81%. Removal of protected group of **12** by hydrogenolysis afforded (+)-trachelanthic acid (**13**), whose structure was also supported by ^{1}H NMR and ^{13}C NMR spectra. The resulting acid **13** was converted to the acetonide **14** by treatment of 20 equiv of 2,2-dimethoxypropane and a trace amount of concd hydrochloric acid in a yield of 90%. (−)-Trachelanthic acid (**16**) was synthesized from **15** by the same sequence used for the synthesis of (+)-trachelanthic acid. Compound **16** was identical in all respects with **13** except for the sign of the specific rotation. The acid **16** was transformed into the acetonide **17** by a similar treatment mentioned above. The first enantioselective syntheses of **13** and **16** have thus been achieved by the convergent method employing D- and L-arabinose as a chiral source.

Total Syntheses of Indicine *N*-Oxide, Intermedine *N*-Oxide, Their Enantiomers, and Their Analogues. The first synthesis of hepatotoxic pyrrolizidine alkaloid was reported in the reconstruction of intermedine (**22**) by coupling 1-(chloromethyl)-1,2-dehydro-7β-hydroxy-8α-pyrrolizidine and (+)-trachelanthic acid sodium salt obtained from natural source in a low yield.[7]

For syntheses of **1**, **3**, **4**, and **5**, the coupling each of **18** and **19** with each of **14** and **17** was examined by regioselective esterification. The synthetic approaches to monoester pyrrolizidine alkaloids have been described by use of combinations of 1,1′-carbonyldiimidazole (CDI) and imidazoylsodium in tetrahydrofuran,[14] dicyclohexylcarbodiimide (DCC) and catalytic amount of 4-(dimethylamino)pyridine (DMAP) in toluene,[15] and CDI and a catalytic amount of imdiazoylsodium in *N*,*N*-dimethylformamide.[6] These studies suggested that the combination of DCC and DMAP was most suitable for our synthesis.

Treatment of **14** and **19** with DCC and DMAP in toluene followed by hydrolysis with 0.6 M hydrochloric acid afforded foamy (−)-indicine (**20**) (71% yield), identical in all respects with natural indicine[16] except for the sign of the specific rotation. Oxidation of **20** with *m*-chloroperbenzoic acid (MCPBA) in dry acetone gave **3** (84% yield), whose spectral properties were superimposable with those of natural indicine



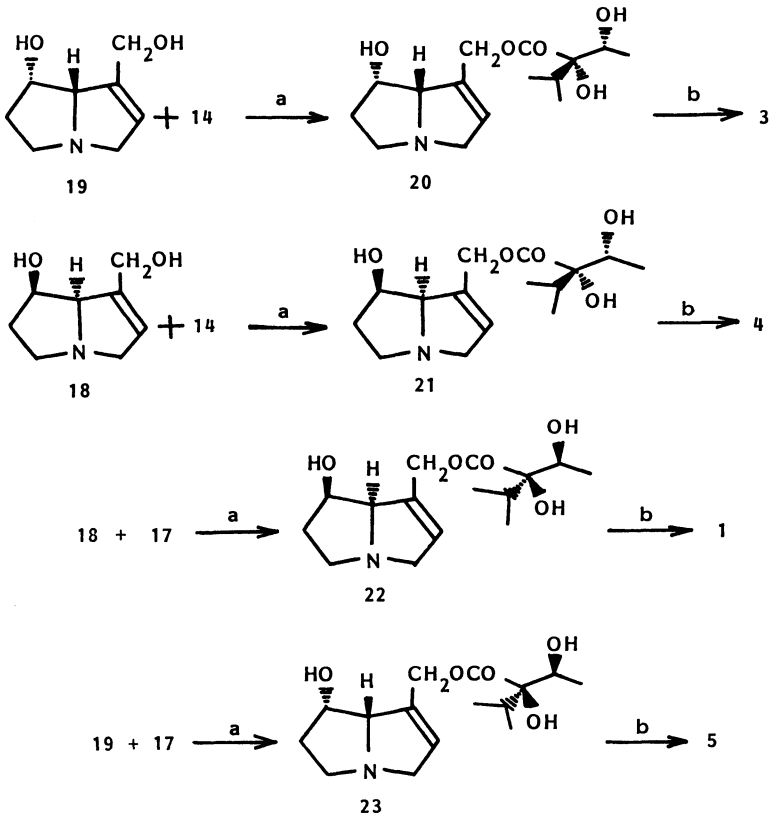
a) $(CH_3)_2CHMgBr/Et_2O$ (52%); b) NaH/DMF, then BzlCl (94%); c) i) 6 M HCl–AcOH (1:3); ii) Ac_2O/Py (90%); d) $NaBH_4$/EtOH, Δ (72%); e) $NaIO_4/KMnO_4/Na_2CO_3$/*t*-BuOH–H_2O (81%); f) H_2/10% Pd–C/MeOH (90%); g) $(CH_3)_2C(OCH_3)_2$/trace concd HCl (90%)

Scheme 1.

N-oxide.[16]

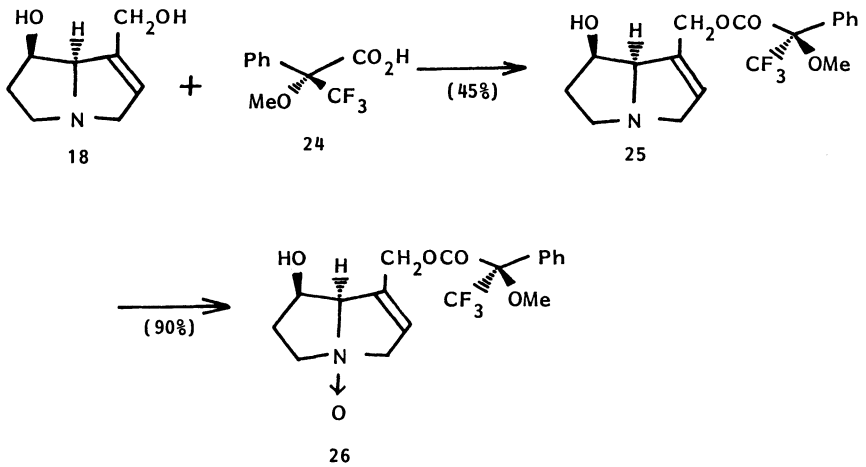
The synthesis of intermedine *N*-oxide (**4**) was achieved through the same sequence used for the synthesis of (−)-indicine *N*-oxide. Esterification of **18** with **14** followed by acid hydrolysis produced intermedine (**21**) (76% yield), identical in all respects with natural intermedine.[17] Oxidation of **21** with MCPBA in dry acetone afforded hygroscopic **4** quantitatively, whose structure was confirmed by ^{1}H NMR, ^{13}C NMR, IR, and mass spectra.

The synthesis of indicine *N*-oxide (**1**) from **18** and **17**, and the synthesis of (−)-intermedine *N*-oxide (**5**) from **19** and **17** were accomplished via indicine (**22**) and (−)-intermedine (**23**) by the same sequence used for the syntheses of **3** and **4**, respectively. The spectral properties of all of synthesized compounds were superimposable with those of natural specimens.[16,17] Thus, the diastereomeric set, which is composed of



a) DCC/DMAP/PhCH$_3$, then 0.6 M HCl (71%);
b) mCPBA/CH$_3$COCH$_3$ (84%)

Scheme 2.



Scheme 3.

Table 1. The Antitumor Activity in Vitro Test (Inhibition/%)

Compound	Dose / μg ml^{-1}	IMC[a] / carcinoma	Tumor cell		
			P388	P388/ADR[b]	L1210
Indicine *N*-oxide (**1**)	100	42	77	57	10
	25	14	45	15	6
(−)-Indicine *N*-oxide (**3**)	100	42	0	0	0
	25	18	0	0	0
Intermedine *N*-oxide (**4**)	100	42	0	0	0
	25	22	0	0	0
(−)-Intermedine *N*-oxide (**5**)	100	42	0	0	0
	25	15	0	0	0
Compound **26**	100	82	75	33	76
	25	74	51	0	61

a) Mouse mammary carcinoma cells. b) Adriamycin-resistant P388 cells.

two enantiomeric pairs related to **1**, has successfully been synthesized.

In relation to these syntheses, we were interested in the synthesis of new analogue modeled on **1**. The antitumor activity of four diastereomers and indicine *N*-oxide derivatives[3b,18] suggested that the electronic and steric factor around α-carbon of necic acid esterified to (+)-retronecine played an important role in increasing antitumor activity. In view of these facts, we undertook to synthesize **26**. Treatment of **18** and **24** with DCC and DMAP in toluene gave 9-*O*-[(*S*)-(−)-2-methoxy-2-phenyl-3,3,3-trifluoropropionyl]retronecine (**25**) in a yield of 68%. Oxidation of **25** resulted in **26** (90% yield).

The antitumor activity of synthesized compounds is shown in Table 1. Among four diastereomers synthesized, **1** showed the best antitumor activity. Interestingly, the synthesized analogue **26** was found to have the superior activity to **1**.

Experimental

General Methods. Melting points were determined with a Yamato apparatus and were uncorrected. IR spectra were determined on a Hitachi Model 260-10 spectrophotometer. Optical rotations were measured with a Parkin-Elmer Model 241 polarimeter. The ^{1}H NMR spectra were recorded with Varian XL-100, Varian EM-390, Bruker WM250, and Jeol GX-400 spectrometers. Chemical shifts were expressed in values (ppm) with tetramethylsilane as an internal standard. Proton noise decoupled FT ^{13}C NMR spectra were taken at 100.4 MHz on a Jeol GX-400 spectrometer using tetramethylsilane as a reference. The mass spectra were taken by a Hitachi RMU-6M mass spectrometer for electron-impact ionization or RMU-7M for field-desorption and for secondary ionization.

1,2-*O*-Isopropylidene-5-deoxy-3-*C*-isopropyl-β-D-lyxofuranose (7). To a solution of **6** (1.3 g) in diethyl ether (26 ml) was added isopropylmagnesium bromide in ether (1 mol dm^{-3}, 13 ml) at −78 °C, and the mixture was stirred from −78 °C to room temperature, and then the mixture was stirred at room temp overnight. After addition of water, the reaction mixture was extracted with ether. The extract was washed with NaCl-saturated aqueous solution, dried over $MgSO_4$, and filtered. Evaporation of the filtrate to give a solid, which was subjected to the column chromatography on silic gel. Elution with toluene–acetone (10:1) gave solids of **7** (849 mg, 52%) and **8** (572 mg, 35%). **7**: mp 37.5—38.5 °C; $[\alpha]_D^{20}$ +9.8° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3540, 3000, 2970, 2940, 2880, 1470, 1460, 1390, 1380 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ=0.96 (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 Hz, H-1); MS (EI) *m/z* 217 (M$^+$+1), 261, 215, 183.

1,2-*O*-Isopropylidene-3-*O*-benzyl-5-deoxy-3-*C*-isopropyl-β-D-lyxofuranose (9). To a solution of **7** (680 mg) in dry *N*,*N*-dimethylformamide (6.8 ml) was added NaH (50% in oil, 375 mg) at 0 °C. After the mixture was stirred at room temperature for 30 min, benzyl chloride (1.08 ml) was added to the mixture. Then the resulting mixture was stirred at room temperature overnight. After being quenched with water, evaporation of the solvent gave an oil. The oil was dissolved in chloroform, and the chloroform solution was washed with water, dried over $MgSO_4$, and filtered. Evaporation of the solvent gave an oil, which was subjected to the column chromatography on silica gel. Elution with toluene–acetone (10:1) gave an oil of **9** (906 mg, 94%): $[\alpha]_D^{25}$ +15.9° (*c* 0.79, $CHCl_3$); IR ($CHCl_3$) 3000, 2960, 1460, 1390, 1380 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ=0.90 and 0.93 (3H each d, *J*=6.7 Hz, CH_3 of 3-C-isopropyl), 1.27 and 1.57 (3H each s, isopropylidene), 1.37 (3H d, *J*=6.7 Hz, 4-CH_3), 2.27 (1H heptet, *J*=6.7 Hz, CH of 3-C-isopropyl), 4.17 (1H q, *J*=6.7 Hz, H-4), 4.43 (1H, d, *J*=4.4 Hz, H-2), 4.43 and 4.67 (2H ABq, CH_2-φ), 5.68 (1H, d, *J*=4.4 Hz, H-1) and 7.2—7.6 (5H m, phenyl); MS (SIMS) *m/z* 329 (M$^+$+Na), 249, 143, 59, 43; (EI) *m/z* 305 (M$^+$−1), 291, 261, 248.

1,2-Di-*O*-acetyl-3-*O*-benzyl-5-deoxy-3-*C*-isopropyl-D-lyxofuranose (10). Compound **9** (840 mg) was dissolved in a mixture of 70% acetic acid–6 M[†] hydrochloric acid (4:1, 10 ml), and the mixture was allowed to stand at room temp for 2 h. After being neutralized with solid Na_2CO_3, the mixture was filtered, and the residue was washed with

† 1 M=1 mol dm^{-3}.

acetone. The filtrate and washings were combined, and evaporated to dryness to give an oil. To a solution of the oil in pyridine (12 ml) was added acetic anhydride (4 ml), and the mixture was allowed to stand at room temperature overnight. After being quenched with water, evaporation of the solvent gave a solid, which was dissolved in chloroform. The solution was washed with water, and dried over $MgSO_4$. Evaporation of the solvent gave an oil. The oil was subjected to the column chromatography on silica gel. Elution with toluene–acetone (10:1) gave the α-acetate of **10** (807 mg, 84%) and the β-acetate of **10** (58 mg, 6%). α-Acetate of **10**: $[\alpha]_D^{27}$ +62.7° (*c* 0.73, $CHCl_3$); IR ($CHCl_3$) 3030, 2980, 2950, 2880, 1750, 1375, 1250 (sh) cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ=1.00 and 1.03 (3H each d, *J*=6.7 Hz, CH_3 of 3-C-isopropyl), 1.38 (3H d, *J*=6.7 Hz, 4-CH_3), 1.97 and 2.10 (3H each s, isopropylidene), 4.38 (1H q, *J*=6.7 Hz, H-4), 4.73 and 4.90 (2H ABq, *J*=12 Hz, CH_2-ϕ), 5.53 (1H d, *J*=3 Hz, H-2), 6.18 (1H d, *J*=3 Hz, H-1) and 7.2—7.6 (5H m, phenyl), MS (SIMS) *m/z* 373 (M^++Na), 291, 185, 142, 91, 84, 43.

β-Acetate of **10**: $[\alpha]_D^{27}$ +3.9° (*c* 0.55, $CHCl_3$); IR ($CHCl_3$) 3030, 2975, 2950, 2880, 1750, 1380, 1250 (sh) cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ=1.00 and 1.05 (3H each d, *J*=7.0 Hz, CH_3 of 3-C-isopropyl), 1.40 (3H d, *J*=6.7 Hz, 4-CH_3), 1.97 and 2.0 (3H each s, -$COCH_3$), 2.37 (1H heptet, *J*=7.0 Hz, CH of 3-C-isopropyl), 4.23 (1H q, *J*=6.7 Hz, H-4), 4.62 and 4.83 (2H ABq, CH_2-ϕ), 5.42 (1H d, *J*=5.1 Hz, H-2), 6.26 (1H d, *J*=5.1 Hz, H-1) and 7.1—7.6 (5H m, phenyl), MS (SIMS) *m/z* 373 (M^++Na), 291, 185, 142, 91, 84.

(2*R*,3*S*,4*R*)-3-Benzyloxy-3-isopropyl-1,2,3,4-pentanetetrol (11). To a solution of **10** (816 mg) in ethanol (15 ml) was added $NaBH_4$ (2.64 g), and the mixture was stirred at room temperature overnight, and then refluxed under stirring for 20 h. After being quenched with acetic acid, evaporation of the solvent gave a solid. The solid was extracted with warm ethyl acetate, and the extract was evaporated to give an oil. The oil was subjected to the column chromatography on silica gel to give an oil of **11** (450 mg, 72%): $[\alpha]_D^{25}$ +6.8° (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) 3560, 3420, 2970, 2940, 2880, 1460, 1380 (sh) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ=1.08 and 1.17 (3H each d, *J*=7.2 Hz, CH_3 of isopropyl), 1.39 (3H d, *J*=6.8 Hz, H-5), 2.25 (3H heptet, *J*=7.2 Hz, CH of isopropyl), 3.78 (1H dd, *J*=7.0 and 12 Hz, H-1), 3.91 (1H dd, *J*=3.6 and 12 Hz, H-1′), 4.13 (1H dd, *J*=3.6 and 7.0 Hz, H-2), 4.16 (1H q, *J*=6.8 Hz, H-4), 4.67 and 4.81 (2H ABq, *J*=11.2 Hz, CH_2-ϕ); MS (FD) *m/z* 268 (M^+), 223, 207, 149, 91, 61, 58, 32.

2-*O*-Benzyl-(+)-trachelanthic Acid (12). To a solution of **11** (330 mg) in *t*-butyl alcohol (5 ml) was added a solution of mixture of $NaIO_4$ (610 mg) and $KMnO_4$ (41 mg) in water (14 ml) and K_2CO_3, and the mixture was stirred at room temperature for 1 h. After being acidified with 1 M sulfuric acid, the mixture was extracted with dichloromethane. The extract was dried over $MgSO_4$, and filtered. The filtrate was evaporated to give an oil. The oil was subjected to the preparative thin-layer chromatography on silica gel developed with chloroform–methanol (9:1) to give an oil of **12** (252 mg, 81%): $[\alpha]_D^{25}$ −16.47° (*c* 0.87, $CHCl_3$); IR ($CHCl_3$) 3350, 2980, 2940, 2880, 1600, 1460, 1400 (sh) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ=0.96 and 1.02 (3H each d, *J*=7 Hz, CH_3 of isopropyl), 1.15 (3H d, *J*=7.0 Hz, H-4), 2.0—2.2 (1H broad m, CH of isopropyl), 4.17 (1H q, *J*=7.0 Hz, H-3), 4.59 and 4.74 (2H ABq, *J*=11.6 Hz, CH_2-ϕ); ^{13}C NMR ($CDCl_3$) δ=18.112, 18.629, 18.825 (3×CH_3), 31.903 (CH of isopropyl), 67.195 (CH_2-ϕ), 69.517 (C-3), 88.176 (C-2) and 178.509 (C-1); MS (FD) *m/z* 253 (M^+), 159, 58, 23.

(+)-Trachelanthic Acid (13). Compound **12** (173 mg) in methanol (17 ml) was stirred with 10% Pd/C (50 mg) under bubbling hydrogen gas at room temperature for 3 h. The catalyst was filtered off, and the filtrate was evaporated to give an oil. The oil was dissolved in 1 M hydrochloric acid, and the solution was extracted with ether. The extract was washed with NaCl-saturated aqueous solution, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a solid. The solid was crystallized from benzene–hexane to yield a crystal of **13** (100 mg, 90%): mp 89.5—90 °C; $[\alpha]_D^{25}$ +4.0° (*c* 0.85, EtOH); IR ($CHCl_3$) 3500, 3040, 2980, 2950, 2890, 1720, 1475, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ=0.96 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); ^{13}C NMR ($CDCl_3$) δ=16.741, 16.825 and 16.881 (3×CH_3), 32.771 (CH of isopropyl), 69.656 (C-3), 82.567 (C-2) and 177.348 (C-1); MS (SIMS) *m/z* 163 (M^++1), 75, 57, 45.

2,3-*O*-Isopropylidene-(+)-trachelanthic Acid (14). To a solution of **13** (89 mg) in 2,2-dimethoxypropane (1.78 ml) was added concd hydrochloric acid (14 μl), and the mixture was allowed to stand at room temperature ovenight. Evaporation of the solvent gave an oil, which was solidified with ether. The solid was subjected to the preparative thin-layer chromatography developed with chloroform–methanol (3:1) to give a solid. The sublimation of the solid gave a crystal of **14** (100 mg, 90%): mp 54.5—55.5 °C; $[\alpha]_D^{25}$ −34.2° (*c* 0.35, EtOH); IR ($CHCl_3$) 2980, 2940, 2875, 1770, 1720, 1460, 1390, 1380, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ=0.91 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); MS (SIMS) *m/z* 203 (M^++1) 162, 75, 57, 45.

(−)-Trachelanthic Acid (16). Procedures used for the synthesis from **15** were similar to those used for the preparation of **13** from **6**; the yield 93%: mp 89.5—90 °C; $[\alpha]_D^{25}$ −4.8° (*c* 0.51, EtOH).

2,3-*O*-Isopropylidene-(+)-trachelanthic Acid (17). Procedure employed was similar to that used for the preparation of **14** from **13** described above; the yield 88%: mp 55—56 °C; $[\alpha]_D^{25}$ +36° (*c* 0.31, EtOH).

(−)-Indicine (20). To a solution of mixture of (+)-retronecine (**18**, 21.5 mg) and **14** (46 mg) in toluene (3 ml) was added DCC (46.6 mg) and DMAP (3.35 mg), and the mixture was stirred at room temperature for 3 d. The precipitate was filtered off, and the residue was washed with a small amount of toluene. The filtrate was extracted with 0.6 M hydrochloric acid. The extract was allowed to stand at room temperature for 8 h. After being made basic by treatment with 28% NH_4OH solution, the mixture was treated with solid NaCl until saturation, and then the mixture was extracted with ether. The extract was dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a foamy glass, which was subjected to the preparative thin-layer chromatography on silica gel developed with chloroform–methanol–concd aqueous ammonia (10:3:0.1) to give a foamy glass of **20** (29.4 mg, 71%): $[\alpha]_D^{23}$ −19° (*c* 2.6, EtOH); IR ($CHCl_3$) 3500 (br), 2975, 2950, 2875, 1730, 1475, 1460, 1390, 1380, 1325, 1305, 1230 (sho), 1180, 1160, 1110, 1080, 1035, 1005, 975, 890, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ=0.92 and 0.97 (3H each d, *J*=7 Hz, CH_3 of isopropyl), 1.17 (3H d, *J*=6.7 Hz, H-13), 1.85—2.05 (2H m,

H-6,6'), 2.15 (1H heptet, J=7 Hz, CH of isopropyl), 2.65—2.85 (1H m, H-5), 3.2—3.35 (1H m, H-5'), 3.42 (1H dd, J=5.2 and 15.6 Hz, H-3), 3.96 (1H d, J=15.6 Hz, H-3'), 4.04 (1H q, J=6.7 Hz, H-12), 4.16 (1H broad s, H-8), 4.28 (1H broad s, H-7), 4.59 and 5.09 (2H ABq, J=12.4 Hz, H-9) and 5.91 (1H s, H-2); ^{13}C NMR ($CDCl_3$) δ=16.564, 17.166, 17.543 (3×CH_3), 32.345 (CH of isopropyl), 36.248 (C-6), 53.777 (C-5), 62.885 (C-3), 63.011 (C-9), 69.194 (C-12(?)), 71.321 (C-8), 78,679 (C-7(?)), 82.764 (C-11), 130.428 (C-2), 132.806 (C-1) and 175.364 (C-10); MS (SIMS) m/z 300 (M^++1), 138, 94, 80, 43: (FD) 299 (M^+), 262, 220, 186, 99, 58.

(−)-Indicine *N*-Oxide (3). To a solution of **20** (25 mg) in dry acetone (1.5 ml) was added MCPBA (18 mg), and the mixture was stirred at room temperature for 1 h. The mixture was directly subjected to the preparative thin-layer chromatography on silica gel to give a solid. The solid was crystallized from a mixture of acetone–methanol to yield a crystal of **3** (22.2 mg, 84%): mp 119—121 °C; $[\alpha]_D^{21}$ −34.7° (c 1.44, EtOH); IR ($CHCl_3$) 3300 (br), 2980, 2950 (sh), 1740, 1460 (sh), 1380, 1310 (sh), 1230 (br), 1185, 1165, 1145, 1100, 1060, 1025, 1010, 990, 950, 890, 835 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ=0.90 and 0.94 (3H each d, J=7 Hz, CH_3 of isopropyl), 1.15 (3H d, J=6.7 Hz, H-13), 1.88 (1H heptet, J=7 Hz, CH of isopropyl), 2.00 (1H broad m, H-6), 2.59 (1H m, H-6'), 3.65—3.80 (2H m, H-5,5'), 4.08 (1H q, J=6.7 Hz, H-12), 4.42 (1H s, H-3,3'), 4.62 (1H broad s, H-8 (?)), 4.68 (1H s, H-7(?)), 4.70 and 5.05 (2H ABq, J=12.4 Hz, H-9) and 5.81 (1H s, H-2); MS (SIMS) m/z 316 (M^++1), 136, 93, 75, 57, 45.

Intermedine (21). Procedure used was similar to that used for the preparation of **20** from **14** and **19**; the yield 76%: mp 140—141 °C; $[\alpha]_D^{23}$ +6.3 (c 1.2, EtOH); IR ($CHCl_3$) 3500, 2970, 2930, 2850, 1720, 1460 (sh), 1370 (sh), 1320 (sh), 1220 (broad), 1160, 1110, 1080, 1030, 1000, 970, 950, 910, 890, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ=0.93 and 0.94 (3H each d, J=7 Hz, CH_3 of isopropyl), 1.21 (3H d, J=6.7 Hz, H-13), 1.9—2.1 (3H m, H-6,6' and CH of isopropyl), 2.65—2.85 (1H m, H-5), 3.30 (1H t, J=8.4 Hz, H-5'), 3.44 (1H dd, J=6 and 15.4 Hz, H-3), 3.96 (1H d, J=15.4 Hz, H-3'), 4.11 (1H q, J=6.7 Hz, H-12), 4.20 (1H broad s, H-8(?)), 4.27 (1H broad s, H-7(?)), 4.76 and 4.86 (2H ABq, J=12 Hz, H-9) and 5.96 (1H s, H-2); ^{13}C NMR ($CDCl_3$) δ=16.881, 17.118 and 17.244 (3×CH_3), 33.008 (CH of isopropyl), 36.254 (C-6), 53.822 (C-5), 62.537 (C-9), 62.872 (C-3), 69.293 (C-12), 70.901 (C-8), 78.734 (C-7), 83.015 (C-11), 131.203 (C-2), 132.531 (C-1) and 175.278 (C-10).

Intermedine *N*-Oxide (4). Procedure used was similar to that used for the preparation of **3** from **20**: the yield is 98%; $[\alpha]_D^{20}$ +8.6° (c 0.98, EtOH); IR ($CHCl_3$) 3200, 2980 (sh), 1740, 1460 (sh), 1380 (sh), 1310 (sh), 1230 (broad), 1185, 1170, 1145, 1100, 1060, 1025, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ=0.91 and 0.97 (3H each d, J=7 Hz, CH_3 of isopropyl), 1.16 (3H d, J=7 Hz, H-13), 1.85 (1H q, J=6.7 Hz, CH of isopropyl), 2.01 (1H broad d, J=11 Hz, H-6), 2.45—2.65 (1H m, H-6'), 3.75—3.85 (2H m, H-5,5'), 4.11 (1H q, J=6.7 Hz, H-12), 4.44 (2H broad t, J=18 Hz, H-3,3'(?)), 4.67 (1H broad s, H-8(?)), 4.75 (1H broad s, H-7(?)), 4.85 (2H broad t, J=14 Hz, H-9,9'(?)) and 5.81 (1H s, H-2); ^{13}C NMR ($CDCl_3$) δ=16.741, 17.174 and 17.636 (3×CH_3), 33.722 (CH of isopropyl), 34.701 (C-6), 61.292 (C-5), 69.223 (C-9(?)), 69.559 (C-12(?)), 69.908 (C-8(?)), 77.993 (C-3), 84.064 (C-11), 95.883 (C-7), 122.125 (C-2), 132.811 (C-1) and 174.802 (C-10).

Indicine (22) and Indicine *N*-Oxide (1). Procedures used were similar to those used for the preparations of **3** via **20** from **14** and **19**. **22**: $[\alpha]_D^{22}$ +19.5° (c 1.2, EtOH) [natural indicine[16]: $[\alpha]_D^{22}$ +20° (EtOH)]. **1**: mp 118—119 °C, $[\alpha]_D^{22}$ +35° (c 0.9, EtOH) [natural indicine *N*-oxide:[16] mp 119—120 °C, $[\alpha]_D^{21}$ +34.8° (EtOH)]. Synthetic **22** and **1** were identical in all respects with natural specimens.

(−)-Intermedine (23) and (−)-Intermedine *N*-Oxide (5). Procedures used were similar to those used for the preparation of **4** via **21** from **14** and **18**. **23**: mp 138—139 °C, $[\alpha]_D^{23}$ −7.1° (c 1.1, EtOH). **5**: $[\alpha]_D^{22}$ −9.1° (c 0.88, EtOH).

9-*O*-[(*S*)-(−)-2-Methoxy-2-phenyl-3,3,3-trifluoropropionyl]retronecine (25). To a solution of mixture of (+)-retronecine (**18**, 100 mg) and (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (**24**, Aldrich Chem. Co., 302 mg) in dry toluene (10 ml) was added DCC (240 mg) and DMAP (18 mg), and the mixture was stirred at room temprature overnight. The precipitate was filtered off, and the filtrate was quenched with water. Evaporation of the solvent gave a solid, which was dissolved in dichloromethane. The solution was washed with NaCl-saturated aqueous solution, dried over $MgSO_4$, and filtered. The filtrate was evaporated to give a foamy glass, which was subjected to the preparative thin-layer chromatography on silica gel to give a foamy glass of **25** (169 mg, 68%): $[\alpha]_D^{21}$ −1.9° (c 0.95, $CHCl_3$); IR ($CHCl_3$) 3000, 2950, 2850, 1750, 1460, 1440, 1280, 1250, 1210, 1175 (sh), 1115 (sh), 1085, 1000 (sh), 840 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ=1.6—2.1 (2H m, H-6,6'), 2.4—3.0 (1H m, H-5), 3.1—3.4 (1H m, H-5'), 3.40 (1H dd, J=5.2 and 15.6 Hz, H-3), 3.53 (3H s, OCH_3), 3.93 (1H d, J=15.6 Hz, H-3'), 4.17 (1H broad s, H-7 and H-8), 4.93 (2H broad t, J=14.3 Hz, H-9,9'), 5.85 (1H s, H-2) and 7.2—7.7 (5H m, phenyl); MS (SIMS) m/z 386 (M^++1), 189, 136, 93, 80, 43.

9-*O*-[(*S*)-(−)-2-Methoxy-2-phenyl-3,3,3-trifluoropropionyl]retronecine *N*-Oxide (26). Procedure used was similar to that used for the preparation of **3** from **20**; the yield 90%: $[\alpha]_D^{20}$ +6.0° (c 1.45, $CHCl_3$); IR ($CHCl_3$) 2975 (sh), 1760, 1460, 1280, 1250, 1180 (sh), 1130 (sh), 1020, 1010, 840 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ=2.0 (1H broad d with a small coupling, J=12.6 Hz, H-6), 2.3—2.8 (1H m, H-6'), 3.53 (3H s, OCH_3), 3.5—3.9 (2H m, H-5,5'), 4.42 (2H broad s, H-3,3'), 4.53 (2H broad s, H-7 and H-8), 5.00 (2H broad s, H-9,9'), 5.70 (1H s, H-2) and 7.3—7.7 (5H m, phenyl); MS (SIMS) m/z 388 (M^++1), 189, 136, 93, 80.

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