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INTRAMOLECULAR DOUBLE MICHAEL REACTION III
STEREOSELECTIVE CHIRAL SYNTHESIS OF ATISIRAN-15-ONE

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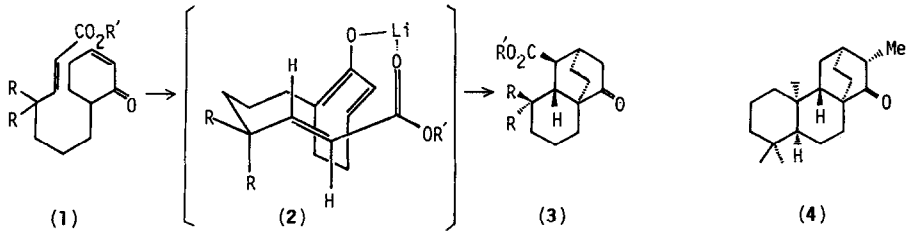
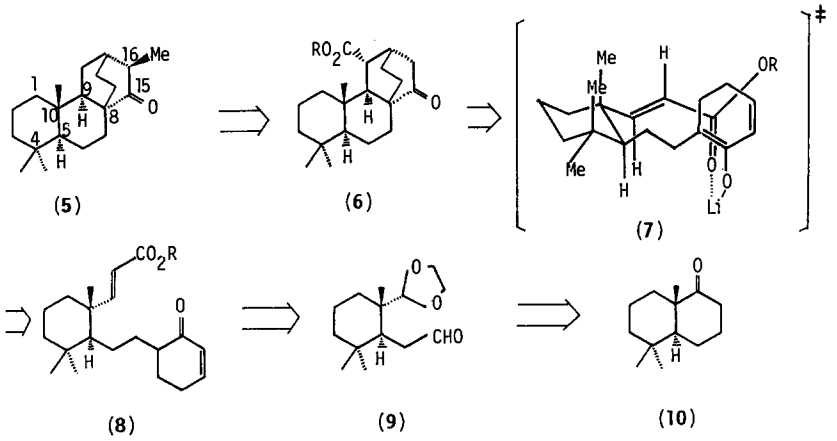
Summary: Atisiran-15-one (**5**) was stereoselectively synthesized starting from the ketone (**10**) through the intramolecular double Michael reaction.

Previously we have shown that the spiro fused bicyclo[2.2.2]octane ring systems (**3**) can be constructed in a highly stereoselective manner by the intramolecular double Michael reaction.[1] The potential importance of this novel reaction prompted us to disclose our own approach to a synthesis of the AB-cis-atisirene type compound (**4**).[2]



We now wish to report the highly stereocontrolled synthesis of atisiran-15-one (**5**)[3] starting from the optically active ketone (**10**) which carries the correct relative stereochemistry between C_5 and C_{10} positions. Our synthetic strategy based upon the retrosynthetic analysis is shown below.

The starting ketone (**10**), $[\alpha]_D^{17}$ -39.10° (c = 0.44, $CHCl_3$), is readily and stereoselectively available in an optically active form from (+)-Wieland-Miescher ketone by the established method.[4] The treatment of **10** with pyridinium hydrobromide perbromide in AcOH at room temperature gave in 99 % yield the bromoketone (**11**),[5,6] m.p. 126 - 128°C, which was transformed into the ketol (**12**)[5,6] in 97 % yield on the action of sodium hydroxide in aqueous DMF.[7] Oxidative cleavage of **12** with lead tetraacetate in MeOH, followed by reduction of the resulting aldehyde obtained in 90 % yield with sodium borohydride furnished, in 97 % yield, the alcohol (**13**).[6] Treatment of **13** with o-nitro-



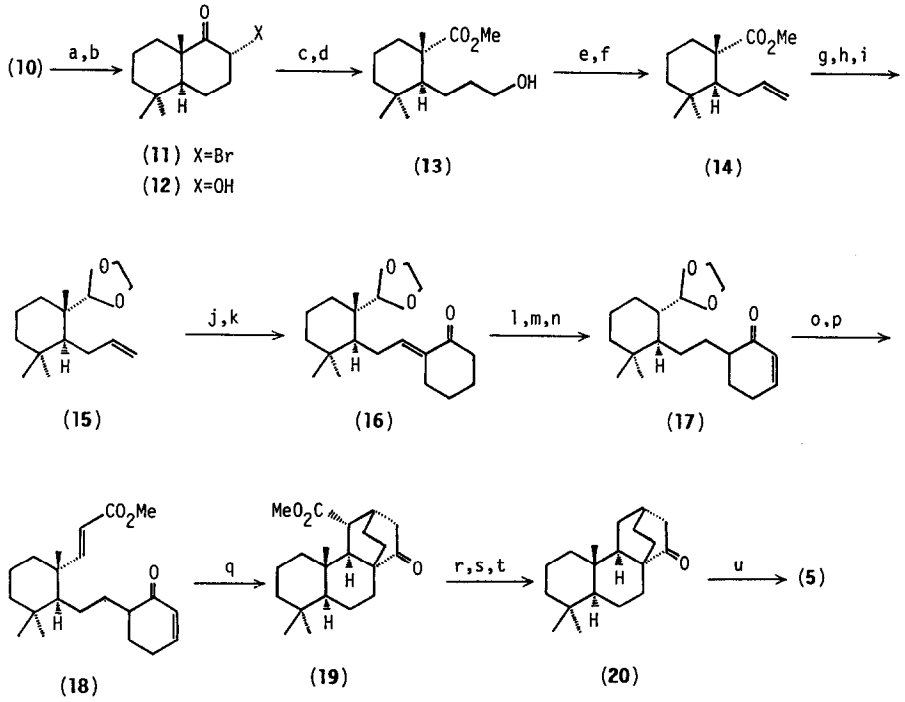
(5) (6) (7) (8) (9) (10)

phenylselenyl cyanide in the presence of tri-n-butylphosphine,[8] followed by oxidation with 30 % H_2O_2 gave the alkene (**14**), $[\alpha]_D^{17}$ +22.9° (c = 0.28, $CHCl_3$). After reduction with lithium aluminum hydride, the alcohol, m.p. 30 - 31°C, $[\alpha]_D^{17}$ +5.0° (c = 0.24, $CHCl_3$), was converted into the acetal (**15**) in 84 % overall yield from the alcohol (**13**) by oxidation with pyridinium chlorochromato followed by acetalization. The olefinic acetal of **15** was oxidatively cleaved with osmium tetroxide and sodium periodate to provide the unstable aldehyde (**9**) in 78 % yield. Aldol condensation of **9** with cyclohexanone was conducted in the presence of lithium diisopropylamide in THF to afford 62 % yield of the enone (**16**),[6] m.p. 52 - 53°C, which was catalytically hydrogenated to furnish quantitatively the corresponding ketone. Formation of the silyl enol ether from the ketone under the kinetically controlled condition, followed by dehydrogenation with palladium acetate in the presence of p-benzoquinone[9] yielded the enone (**17**)[6] in 85 % yield.

Deprotection of the acetal (**17**) afforded 83 % yield of aldehyde, which was then reacted with the Wadsworth-Emmons reagent[10] to form the α,β-unsaturated ester (**18**)[6] as the E-isomer in 47 % yield. The double Michael reaction of **18** was accomplished with lithium hexamethyl-disilazide at -78°C~ room temperature in n-hexane-Et_2O (8:1 v/v) to give the tetracyclic compound (**19**),[6] m.p. 145 - 148°C, $[\alpha]_D^{14}$ -4.0° (c = 0.30, $CHCl_3$), in 53 % yield, as a single isomer. The ester (**19**) was converted into the ketone (**20**) whose IR and NMR spectra were identical with the reported data,[11] by the sequential reactions as previous;[2] reduction of **19** with diisobutylaluminum hydride followed by oxidation with pyridinium dichromate and the decarbonylation[12] of the ketoaldehyde, m.p. 150 - 151°C, with tris(triphenylphosphine)chlororhodium. Methylation of **20** with methyl iodide in the presence of lithium diisopropylamide at -78 0°C furnished atisiran-15-one (**5**) as a single isomer, whose spectral data were consistent with reparted ones.[3]

Further application of the intramolecular double Michael reaction to other natural products is in progress.

Scheme



reagents: (a) Py HBr Br_2/AcOH (b) NaOH/DMF-H_2O (c) $Pb(OAc)_4$/MeOH-C_6H_6 (d) $NaBH_4$/MeOH (e) o-$C_6H_4(NO_2)SeCN$, $^nBu_3P$/THF (f) 30 % H_2O_2/THF (g) LAH/Et_2O (h) PCC/CH_2Cl_2 (i) HO⌒OH, TsOH/C_6H_6 (j) OsO_4, $NaIO_4$ (k) cyclohexanone, LDA/THF (l) H_2, Pd-C/EtOH (m) LDA then TMSCl (n) $Pd(OAc)_2$, p-benzoquinone/CH_3CN (o) 10 % $HClO_4$/THF (p) $(MeO)_2\overset{O}{\overset{\|}{P}}CH_2CO_2Me$, NaH/DME (q) LiN(TMS)$_2$/n-hexane-$Et_2O$ (r) DIBAL-H/CH_2Cl_2 (s)PDC/DMF (t) $(Ph_3P)_3RhCl$/xylene (u) MeI, LDA/THF

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(5) The compound is more thermodynamically stable isomer.

(6) All compounds have been characterized by elemental analysis and/or high resolution mass spectra. Significant spectral data are reported below: (**11**) IR ν max ($CHCl_3$) 1720 cm^{-1} (CO); ^{1}H-NMR ($CHCl_3$) δ 0.90, 0.91, 1.17 (each 3H, each s, 3 Me), 4.94 (1H, dd, J 5.7, 11.4 Hz, C<u>H</u>Br). (**12**) IR ν max ($CHCl_3$) 3470 cm^{-1} (OH), 1700 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ 0.91, 0.93, 1.16 (each 3H, each s, 3 × Me), 4.38 (1H, ddd, J 3.4, 7.1, 11.4, Hz, C<u>H</u>OH). (**13**) IR ν max ($CHCl_3$) 3600 cm^1 (OH), 1715 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ 0.89, 0.93, 1.19 (each 3H, each s, 3 × Me), 3.56 (2H, bt, J 5.7 Hz, $-CH_2O-$), 3.64 (3H, s, OMe). (**16**) IR ν max ($CHCl_3$) 1670 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ 0.84, 0.90, 0.97 (each 3H, each s, 3 × Me), 4.43 (1H, s, $-CH<^{O-}_{O-}$), 6.69 (1H, tt, J 1.4, 6.6 Hz, -CH=). (**17**) IR ν max ($CHCl_3$) 1670 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ 0.88 (3H, s, Me), 0.90 (6H, s, 2 × Me), 5.85 (1H, bd, J 10 Hz, -COCH=), 6.55 - 6.97 (1H, m, =C<u>H</u>CH_2-). (**18**) IR ν max ($CHCl_3$) 1710, 1670 cm^{-1} (CO); ^{1}H-NMR (CCl_4) δ 0.92, 0.95, 1.05 (each 3H, each s, 3 × Me), 3.67 (3H, s, OMe), 5.53 (1H, d, J 16 Hz, =$CHCO_2$Me), 5.78 (1H, bd, J 10 Hz, -COCH=), 6.53 - 6.95 (1H, m, $-CH_2$C<u>H</u>=), 6.72 (1H, d, J 16 Hz, -C<u>H</u>=$CHCO_2$Me). (**19**) IR ν max ($CHCl_3$) 1725, 1715 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$) δ 0.82, 0.88, 1.02 (each 3H, each s, 3 × Me), 3.61 (3H, s, OMe).

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