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Enantioselective Synthesis of (-)-Elenolic Acid and (-)-Ajmalicine

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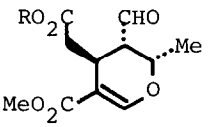
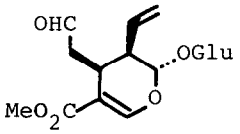
Summary: A secoiridoid monoterpene (-)-elenolic acid and a representative heteroyohimbine alkaloid (-)-ajmalicine have been synthesized enantio- and stereoselectively using L-ethyl lactate as a chiral starting material.

Elenolic acid (1) is a secoiridoid monoterpene isolated from olive (Olea europea).[1] It is biologically closely related to secologanin (4) and contains a tetrasubstituted dihydropyran system as a characteristic structural element in common with ajmalicine (5) and sarracenin (6). The synthesis[2,3] of elenolic acid derivatives (1-3), particularly methyl elenolate (2), has attracted great attention not only because of their broad range antiviral activity[4] but also their synthetic utility[5] as a precursor of ajmalicine (5), a therapeutically important heteroyohimbine alkaloid. We now wish to report a chiral synthesis of (-)-elenolic acid (1) and its derivative (-)-methyl elenolate (2) from L-ethyl lactate (7) and also to report conversion of 2 to (-)-ajmalicine (5).



1, R=H
2, R=Me 3, R=Ca/2



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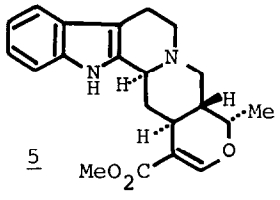

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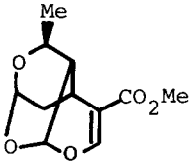

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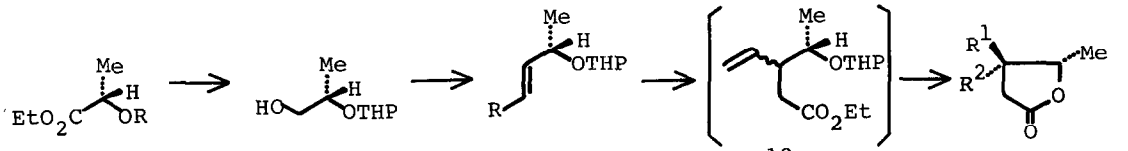
L-Ethyl lactate (7) was converted to the tetrahydropyranyl ether 8 (DHP, PPTS, CH_2Cl_2, rt) which, upon reduction with lithium aluminum hydride (THF, -50 °C), gave the alcohol 9.[6] Swern oxidation of 9 followed by Horner-Emons reaction using triethyl phosphonoacetate (NaH, THF, -78 °C) afforded the E-unsaturated ester 10 which was then reduced with aluminum hydride (Et_2O, -60 °C) to give the allylic alcohol 11 in 80% overall yield from 7. Ortho-ester Claisen rearrangement[7] of 11 using ethyl orthoacetate (cat. $^tBuCO_2H$, 140 °C) followed by treatment with pyridinium p-toluenesulfonate (EtOH, reflux) provided the cis-γ-lactone 13,[8] bp_{25} 110 °C (Kugelrohr), $[\alpha]_D$ -54.3° ($CHCl_3$), δ ($CDCl_3$): 1.30 (3H, d, J=7 Hz), 4.68 (1H, quint, J=7 Hz), and trans-γ-lactone 14, bp_{20} 130 °C (Kuglrohr), $[\alpha]_D$ -75.9° ($CHCl_3$), δ ($CDCl_3$): 1.38 (3H, d, J=7 Hz), 4.25 (1H, d quint, J=2 and 7 Hz), in a ratio of 3 : 1 in 60% overall yield from 11. Although this type of allylic alkoxy directed Claisen rearrangement

has not been examined in view of diastereofacial selection so far,[10] one might rationalize the production of the cis-γ-lactone 13 as the major product of this reaction sequence by assuming a transition state resembling either "inside alkoxy model" or "Felkin type model".[11]



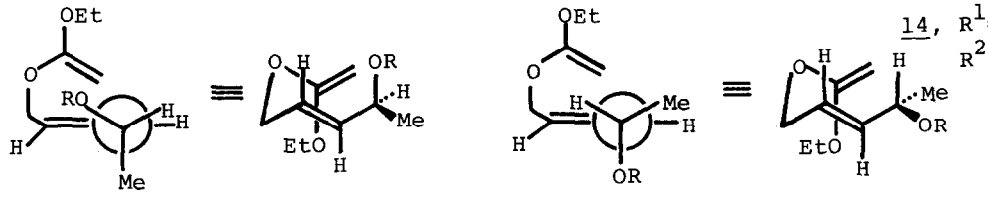
7, R=H
8, R=THP

9

10, R=CO_2Et
11, R=CH_2OH

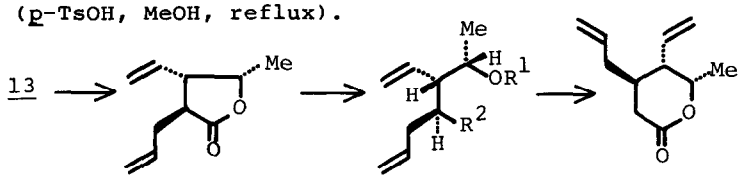
12

13, R^1=H, R^2=CH=CH_2
14, R^1=CH=CH_2, R^2=H



"inside alkoxy model" "Felkin type model" R=THP

Then, according to the method established previously,[9] the cis-γ-lactone 13 was transformed into the key chiral δ-lactone 18, $[\alpha]_D$ -81.0° ($CHCl_3$), in 55% overall yield by the following sequence: (1) stereoselective alkylation of 13 using allyl bromide (LDA, THF, -78 °C); (2) lactone to lactol reduction (DIBAL, CH_2Cl_2, -78 °C) and Wittig reaction using α-methoxymethylenetriphenylphosphorane (glyme, rt); (3) protection ($^tBuMe_2SiCl$, imidazole, DMF, rt) and oxidation[12] with pyridinium chlorochromate (CH_2Cl_2, rt); (4) acidic methanolysis (p-TsOH, MeOH, reflux).



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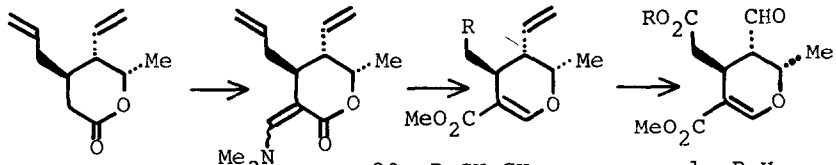
16, R^1=H, R^2=HC=CHOMe
17, R^1=$^tBuMe_2Si$, R^2=CH_2CO_2Me

18

Heating the lactone 18 with N,N-dimethylformamide dimethyl acetal in a sealed tube (170 °C, 3 days) gave the vinylogous urethane 19 which was successively subjected to acid hydrolysis (1N-HCl, Et_2O, rt) and acyl-lactone rearrangement[13] (5% H_2SO_4-MeOH, reflux) to afford the dyhydropyran 20, $[\alpha]_D$ -208.8° ($CHCl_3$), in 55% overall yield from 18. Treatment of 20 with one molar equivalent of osmium tetroxide (pyridine, 0 °C) followed by reductive work-up (2% $NaHSO_3$, rt) allowed highly selective hydroxylation at the double bond of the allyl substituent to give a 8 : 7 epimeric mixture of the diol 21. The diol 21 was then cleaved with lead tetraacetate (THF, 0 °C) to the aldehyde 22 which was directly converted to the acid 23, $[\alpha]_D$ -121.7° ($CHCl_3$), by Jones oxidation in 65% overall yield from 20.

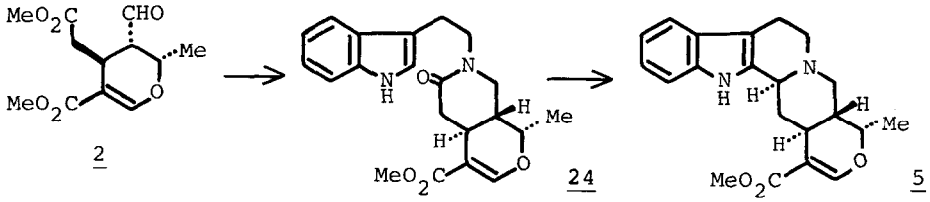
Finally, Lemieux-Johnson oxidation[14] of 23 (10 mol % OsO_4, 2.5 equiv.



18 19 20, R=CH=CH$_2$ 21, R=CH(OH)CH$_2$OH 22, R=CHO 23, R=CO$_2$H 1, R=H 2, R=Me

$NaIO_4$, aq. THF, 0 °C) furnished (-)-elenolic acid (1), $[\alpha]_D$ -77.7° ($CHCl_3$), in 40-55% yield (50-65% yield based on the consumed 23).[15, 16] Synthetic 1 exhibited spectral properties (^{1}H-NMR, IR, MS) in accord with those of natural substance.[17] Further identy of the synthesis of 1 was established by the fact that esterification of 1 (CH_2N_2, Et_2O, rt) gave (-)-methyl elenolate (2) quantitatively. The spectral data (^{1}H-NMR, IR, MS) and the optical rotation of the synthetic material, $[\alpha]_D$ -117.0° ($CHCl_3$), were identical with those of authentic (-)-methyl elenolate (2), $[\alpha]_D$ -111.4° ($CHCl_3$), prepared from natural elenolic acid (1) on treatment with diazomethane.

Furthermore, synthetic (-)-methyl elenolate (2) was converted to (-)-ajmalicine (5) by the basically same procedure as reported by Kelly.[5] Reductive amination[18] of 2 using tryptamine perchlorate ($NaBH_3CN$, MeOH, rt) followed by heating (toluene, reflux) gave the lactam 24, mp 202.0-202.5 °C (lit.[5] 172-174 °C), $[\alpha]_D$ +94.1° ($CHCl_3$), in 79% yield. Bischler-Napieralski cyclization of 24 ($POCl_3$, benzene, reflux) gave the immonium salt which was immediately reduced with sodium borohydride (MeOH, 0 °C) to furnish (-)-ajmalicine (5), mp 257-258 °C (lit.[5] 257 °C), $[\alpha]_D$ -40.2° (MeOH) (lit.[5] -39°), in 45% yield.[19]



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Acknowledgment: We are grateful to Dr. R. C. Kelly (Upjohn Company) for providing us the authentic sample of (-)-calcium elenolate and spectral data (^{1}H-NMR, IR) of (-)-calcium elenolate and (-)-methyl elenolate.

References and Notes:

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10. For example, see: Kametani, T.; Suzuki, T.; Nishimura, M.; Sato, E.; Unno, K. Heterocycles 1982, 19, 205.
11. Arguments based on "inside alkoxy model" and "Felkin type model" have recently been invoked by Houk and Kozikowski to rationalize the stereochemistry of nitrile oxide cycloadditions to chiral allyl ethers: (a) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jager, V.; Schohe, R.; Fronczek, F. R. J. Am. Chem. Soc. 1984, 106, 3880 and references therein; (b) Kozikowski, A. P.; Ghosh, A. K. J. Org. Chem. 1984, 49, 2762 and references therein.
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15. The vinyl side chain of 23 was oxidaized selectively in the early stages of the reaction, but prolonging the reaction time led to over-oxidation of the dihydropyran moiety and diminished the yield of 1. The similar observation was reported in the case of osmylation of secologanin tetraacetate: Purdy, J. R.; Hamilton, R. G.; Alxhter, L.; Mclean, S. Can. J. Chem. 1981, 59, 210.
16. (-)-Elenolic acid (1) was purified as follows: (1) preparative TLC (SiO_2, 0.2% AcOH-Et_2O) using 10% aq. THF for elution; (2) heating in water (80 °C, 15 min.); (3) extraction with methylene chloride. Without the second operation, this material could not be obtained in a pure form presumably because of partial formation of a hemiacetal between the aldehyde and the carboxylic acid residue during preparative TLC.
17. An authentic sample of (-)-elenolic acid (1) was prepared by acidification of (-)-calcium elenolate (3) graciously provided by Dr. R. C. Kelly.
18. Borch, R. F. Org. Syn. 1972, 52, 124.
19. The stereoisomer of 5, presumed to be the C(3)-epimer, was also obtained in 2% yield.

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