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SYNTHETIC STUDIES IN THE QUASSINOID SERIES. CONVERSION OF CHAPARRIN INTO CASTELANONE AND QUASSINOID ANALOGS.

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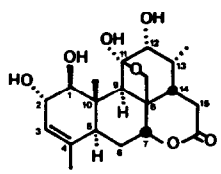
Summary : Inactive chaparrin 1 has been converted in seven steps and in 16 % overall yield to castelanone 3 which is known to inhibit significantly growth of the murine lymphocytic leukemia P-388 cell line. The methodology developed has been applied to the preparation of quassinoid analogs 15, 16 and 17.

As part of our continuing study of the quassinoids [1], a group of biologically active[2,3,4], degraded triterpenes found among plants of the Simaroubaceae, we have been interested in the preparation of antileukemic members of this class starting from abundant, but inactive quassinoid precursors.[5] Thus, while chaparrin 1 [6] is inactive and relatively abundant, the C_{15} esters of glaucarubolone 2 as exemplified by castelanone 3, ailanthinone 4 and glaucarubinone 5 display moderate to strong antileukemic activity in the murine lymphocytic leukemia P-388 test system and are available in only limited quantities from plant sources. [7] We herein report the results of a study aimed at the development of synthetic methodology for



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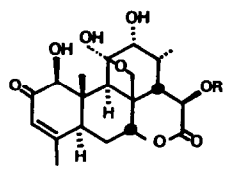


2 R = H
3 R = OCCH$_2$CH(CH$_3$)$_2$
4 R = OCCH(CH$_3$)CH$_2$CH$_3$
5 R = OCC(OH)(CH$_3$)CH$_2$CH$_3$

the conversion of chaparrin 1 into such glaucarubolone ester derivatives and simple analogs in which the C_{15} ester side chain has been replaced by an alkyl group.

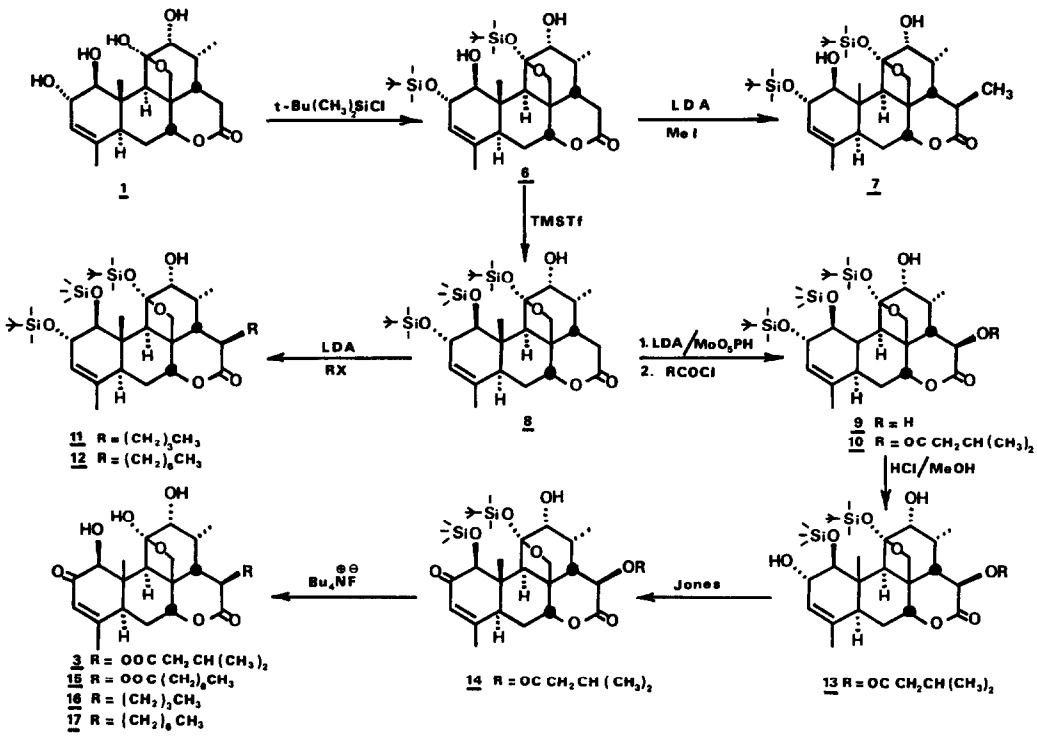
Treatment of chaparrin 1 (see scheme) with excess tert-butyldimethylsilyl chloride [8] in the presence of imidazole (t-Bu$(CH_3)_2$SiCl 10.0 equiv., $C_3H_4N_2$ 12.0 equiv, 0.13 M DMF, R.T., 48 h) afforded the crystalline disilyl derivative 6 (88 %, mp 208-210°C, $[\alpha]_D$ + 26°, c 1.52, $CHCl_3$) whose structure was firmly established on the basis of its 400 MHz ^{1}H-NMR and ^{13}C-NMR spectral data. [9] Although 6 underwent smooth deprotonation with excess lithium diisopropylamide and subsequent alkylation with methyl iodide at - 78°C (LDA 7.0 equiv,

0.05 M THF, -78°C, 2h ; MeI 25 equiv, -78°C, 1h) to afford stereospecifically the 15β-methyl lactone 7 [9] (66 %, mp 215 - 217°C, $[\alpha]_D$ +23°, c 1.52, $CHCl_3$) its derived lithium enolate was unreactive towards the molybdenum peroxide reagent MoO_5-pyridine-HMPA (MoO_5PH)[10] at -78°C and afforded complex product mixtures at higher temperatures. In addition attempted alkylation of the lithium enolate of 6 with poorer electrophiles such as butyl iodide at 0°C gave many products.

Reasoning that base induced intramolecular silyl group migration might be responsible for the complexity of these product mixtures we sought to protect the hydroxyl function at C_1. This could be effected conveniently with trimethylsilyl triflate [11] (TMSTf 3.0 equiv, pyridine 3.1 equiv, 0.10 M $CHCl_3$, R.T., 2h) to afford the trisilyl lactone 8 as a white foam in quantitative yield. Lactone 8 upon treatment with lithium diisopropylamide (LDA 3.0 equiv, 0.09 M THF, -78°C, 2h) and subsequent exposure to MoO_5-pyridine-HMPA (MoO_5PH 3.1 equiv, 0.09 M THF, -44°C, 4h) gave a crude product whose 400 MHz ^{1}H-NMR spectrum indicated a 70:30 mixture of 15-hydroxy lactone 9 and starting material 8. Treatment of this mixture with excess isovaleryl chloride in pyridine-dichloromethane (1:1) (RCOCl 10 equiv, 0.06 M pyr-CH_2Cl_2, R.T., 5h) afforded after chromatography the crystalline ester 10 [9] (mp 182-183°C, $[\alpha]_D$ -32°, c 1.50, $CHCl_3$) in 57 % overall yield from 8. The appearance in the 400 MHz ^{1}H-NMR spectrum of 10, when measured at 50°C, of H_{15} as a broad doublet (J = 11 Hz) at 5.43 ppm is consistent with the natural 15β configuration. Alternatively the lithium enolate derived from 8 could be reacted (RI 5.0 equiv, HMPA 3.0 equiv, 0.11 M THF, 0°C, 4.5 h) with butyl or heptyl iodide to afford alkyl lactones 11 and 12 respectively in greater than 90 % yield.

With lactone ester 10 in hand there remained only to effect desilylation and selective oxidation of the allylic alcohol to complete the preparation of castelanone 3. Unfortunately treatment of 10 with excess tetrabutylammonium fluoride in tetrahydrofuran at ambient temperature resulted in incomplete desilylation and conducting the reaction at higher temperatures led to extensive product decomposition. Our subsequent search for a means of cleanly effecting this deblocking operation was enlivened by the finding that lactone 10 upon exposure to hydrochloric acid in methanol (1N HCl 1.0 equiv, 0.016 M MeOH, R.T., 15 min) underwent selective solvolysis of the t-butyldimethylsilyl group at C_2 to give the allylic alcohol 13 [9]. Jones oxidation of this diol (H_2CrO_4 1.0 equiv, ace 0.015 M, R.T. 3.0 min), isolation and filtration on a short column of silica gel gave disilyl enone 14 in 80 % overall yield from 10. Treatment of 14 with tetrabutylammonium fluoride in tetrahydrofuran (Bu_4NF 2.0 equiv, 0.3 M THF, R.T., 30 min) afforded after chromatography the polar castelanone 3 [9] whose spectral properties and TLC behavior were identical to those of an authentic sample. [12] Although the yield in the final step was disappointingly low (30-45 %) this reaction sequence could be applied with reasonable success to the synthesis of the quassinoid analogs 15-O-octanoyl glaucarubolone 15 and the 15-butyl and 15-heptyl chaparrinones 16 [9] and 17 available from chaparrin 1 in 11, 12 and 33 % overall yields respectively.

Preliminary biological screening of compounds 15, 16 and 17 indicates that all three cause significant inhibition of cell transformation induced by Rous sarcoma virus [4] at the 1 μg/ml level. Further work is underway to assess potential antileukemic properties of these substances.



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2 - Members of this class display a diversity of biological properties ranging from antineoplastic activity to antimalarial action [3] and cell transformation inhibition [4]. For a recent summary of biological data in this area and efforts directed at quassinoid total synthesis, see : Grieco, P.A., Lis, R., Ferrino, S., Yan Jaw, J., J. Org. Chem., 1982, 47, 601, and references cited therein.

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9 - All ^{1}H-NMR spectra were measured at 400 MHz in $CDCl_3$ solution at the normal probe temperature (15-16°C) unless otherwise specified.

6 : NMR δ 5.32 (br s, H_3), 5.01 (d, J=3Hz, 1-OH), 4.34 (br t, J≃3 Hz, H_7), 4.06 (m, H_2), 4.01 (d, J=9 Hz, CH_AH_B), 3.62 (d, J=9 Hz, CH_AH_B), 3.60 (d, J= 4.5 Hz, H_{12}), 3.36 (d,d ; J=3, 8.5 Hz ; H_1), 2.74 (d,d ; J=14, 19 Hz ; $H_{15\alpha}$), 2.70 (s, H_9), 2.60 (d,d ; J=5, 19 Hz ; $H_{15\beta}$), 2.39 (br d, J=13 Hz, H_5), 2.23 (m, H_{13}), 2.08 (br s, 12-OH), 2.04 (d, t ; J=2.5, 15 Hz ; $H_{6\alpha}$), 1.86 (m, H_{14}), 1.75 (br t, J=14.5 Hz, $H_{6\beta}$), 1.67 (s, 4-Me), 1.17 (s, 10-Me), 1.02 (d, J=7 Hz, 13-Me), 0.96 and 0.91 (s, $(CH_3)_3CSi$), 0.26, 0.24, 0.11 and 0.10 (s, CH_3Si). IR ($CHCl_3$) 3560, 2910, 1720, 1165 cm^{-1}.
Anal. Calcd. for $C_{32}H_{56}O_7Si_2$: C, 63.11 ; H, 9.27 ; Found : C, 62.86 ; H, 9.26.

7 : NMR δ 5.30 (br s, H_3), 4.93 (d, J=3 Hz, 1-OH), 4.38 (br t, J≃3 Hz, H_7), 4.03 (m, H_2), 3.96 and 3.58 (2d, J=9 Hz, $-CH_2O-$), 3.58 (m, H_{12}), 3.37 (d,d ; J=3.0, 8.5 Hz ; H_1), 3.01 (d,t ; J=7, 17 Hz ; H_{15}), 2.59 (s, H_9), 2.54 (br d, J=13.5 Hz, H_5), 2.31 (m, H_{13}), 2.08 (br s, 12-OH), 2.00 (d,t ; J=2.5, 14.5 Hz ; $H_{6\alpha}$), 1.72 (br t, J=14.5 Hz, $H_{6\beta}$), 1.61 (s, 4-Me), 1.42 (d, J=7 Hz, 15-Me), 1.18 (d, J=7 Hz, 13-Me), 1.17(s, 10-Me), 0.96 and 0.91 (s, Me_3CSi), 0.25 (s, Me_2Si), 0.10 and 0.09 (s, MeSi).
IR (CCl_4) 3440, 2930, 1740 cm-1.
Anal. Calcd. for $C_{33}H_{58}O_7Si_2$: C, 63.62 ; H, 9.38 ; Found : C, 63.46 ; H, 9.35.

10 : NMR (50°C) δ 5.43 (br d, J=11 Hz, H_{15}), 5.27 (br s, H_3), 4.58 (s, 12-OH), 4.38 (br t, J≃3 Hz, H_7), 3.98 and 3.54 (2d, J=8.5 Hz, $-CH_2O-$), 3.96 (m, H_2), 3.65 (br s, H_{12}), 3.31 (d, J=7.5 Hz, H_1), 2.80 (s, H_9), 2.44 (br d, J=13 Hz, H_5), 2.24 (m, H_{14}), 2.20 (m, CH_2CO_2), 2.12 (m, H_{13}), 2.02 (d,t ; J=2.5, 14 Hz ; $H_{6\alpha}$), 1.72 (br t, J=14 Hz, $H_{6\beta}$) 1.62 (s, 4-Me), 1.16 (s, 10-Me), 1.01 (d, J=7 Hz, 13-Me), 0.98 and 0.89 (s, Me_3CSi) 0.98 (m,Me_2CH), 0.25, 0.22, 0.10 and 0.08 (s, t-BuSiMe), 0.19 (s, Me_3Si).
IR ($CHCl_3$) 3650, 3420, 1735, 1595, 1460 cm^{-1}. Anal. Calcd. for $C_{40}H_{72}O_9Si_3$: C, 61.49, H, 9.29 ; Found : C, 61.75 ; H, 9.35.

13 : NMR δ 5.49 (br m, H_{15}), 5.45 (br s, H_3), 4.98 (br s, OH), 4.46 (br s, H_7), 4.02 and 3.60 (2d, J=8.5 Hz, $-CH_2O-$), 4.02 (m, H_2), 3.67 (br s, H_{12}), 3.35 (d, J=8 Hz, H_1), 2.81 (s, H_9), 2.42 (br d, J=13 Hz, H_5), 2.27 (m, H_{14}), 2.14 (m, H_{13}), 2.06 (br d, J=14 Hz, $H_{6\alpha}$), 1.76 (br t, J=14 Hz, $H_{6\beta}$), 1.66 (4-Me), 1.17 (10-Me), 1.03 (d, J= 7 Hz, 13-Me), 0.99 (m, Me_3CSi and Me_2CH), 0.26 and 0.23 (s, t-BuSiMe), 0.20 (s, Me_3Si)
IR ($CHCl_3$) 3675, 3560, 3400, 2930, 1730, 1600 cm^{-1}. MS (CI, isobutane, pos ion) 649 ($M + H^+ - H_2O$), 631 ($M+H^+-2H_2O$), 577, 559, 547, 517, 133,103,91.

3 : NMR δ 7.82 (br s, OH), 6.13 (br s, H_3), 5.57 (d, J=11 Hz, H_{15}), 5.20 (br s, OH), 4.62 (br s, H_7), 4.07 (s, H_1), 3.95 and 3.69 (2d, J=9 Hz, $-CH_2O-$), 3.56 (d, J=4 Hz, H_{12}), 2.97 (br d, J=13.5 Hz, H_5), 2.75 (s, H_9), 2.41-1.92 (m, 7H), 2.02 (s, 4-Me), 1.21 (s, 10-Me), 1.11 (d, J=7 Hz, 13-Me), 1.00 (d, J=7 Hz, Me_2CH). IR ($CHCl_3$) 3680, 3595, 3290, 2930, 1740, 1675, 1600 cm^{-1}. $[\alpha]_D$ + 62°, c 0.35, $CHCl_3$. MS(CI, isobutane, pos ion) 479 ($M + H^+$), 461 ($M + H^+-H_2O$), 377, 147, 103, 85.

16 : NMR δ 7.76 (br s, OH), 6.12 (br s, H_3), 5.18 (br s, OH), 4.52 (br s, H_7), 4.03 (s, H_1), 3.93 and 3.63 (2d, J=9 Hz, $-CH_2O-$), 3.53 (d, J=4 Hz, H_{12}), 3.02 (m, 2H, H_{15} and H_5), 2.57 (s, H_9), 2.43-1.20 (m, 11H), 2.01 (s, 4-Me), 1.18 (m, 6H, 10-Me and 13-Me), 0.92 (t, J=7 Hz, 4-Me).
IR ($CHCl_3$) 3570, 3275, 2930, 1720, 1675, 1620 cm^{-1}. $[\alpha]_D$ + 42°, c 0.76, $CHCl_3$. MS : Calcd. for $C_{24}H_{34}O_7$: 434.2304 ; Found : 434.2295.

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