Tetrahedron Letters,Vol.27,No.34,pp 3967-3970,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

TOTAL SYNTHESIS OF (±)-ARTEANNUIN B

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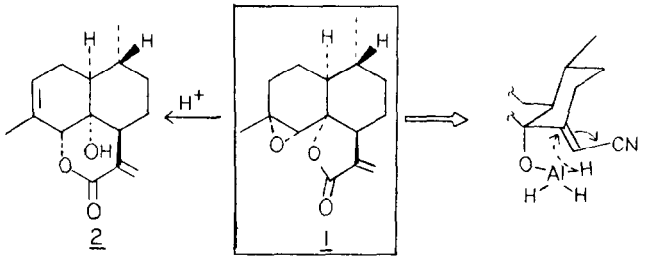
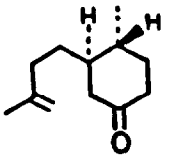
Abstract: The title compound has been synthesized beginning with 4-methyl-2-cyclohexen-1-one, using intramolecular hydroxyl-directed reactions to achieve regio- and stereoselectivity at important stages.

Arteannuin B (1), a major sesquiterpenoid constituent[1] of Artemesia annua L., is an unusual α-methylene-γ-lactone, being trans-fused via a tertiary hydroxyl group at the cis-decalin ring fusion. The strain engendered by this structural feature, inter alia, causes 1 to undergo facile rearrangement[1] to an isomeric δ-lactone (2), under acid catalysis. Thus any synthetic effort[2] toward 1 must avoid acidic conditions once the trans-fused γ-lactone is in place. We recently developed a mechanism-based, intramolecular alkoxyhydride reduction of α,β-unsaturated nitriles for the purpose of diastereoselective trans-γ-lactone annulation.[3] That work involved only secondary hydroxyl directing groups, whereas such an approach to 1 (formulated below) would proceed from a chiral, tertiary hydroxy center.



We describe herein the successful implementation of this strategy, which has resulted in the first total synthesis of (±)-1.

Conjugate addition of 3-methyl-3-butenylmagnesium bromide (with cuprous iodide-dimethyl sulfide) to (±)-4-methyl-2-cyclohexen-1-one[4] afforded cyclohexanone 3[5] in 76% yield (ca. 97% trans isomer, by glc). Electrophilic activation of the side chain and subsequent intramolecular enolate alkylation (S_N2 or S_N2') was achieved (85%) by means of N-chlorosuccinimide[6] (→allylic chloride 4,[5] plus ca. 20% of isomeric vinylic chlorides also cyclizable in part), followed by reaction with freshly-sublimed potassium t-butoxide in THF (2 eqs., 6 h, 25°). Under these conditions, the initially formed cis-decalone isomerized to trans-decalone 5[5] (followed by glc to an equilibrium ratio ca. 13:1), which was purified by distillation (bp 80°/0.02 mm). L-selectride reduction in THF, -10°→25° (>10:1 selectivity) followed by acetylation, gave the axial acetate 6, mp 54-6°, in 90% overall yield. Trifluoroacetic acid addition to 6 (in CH_2Cl_2, -20°) was expected to proceed so as to favor the



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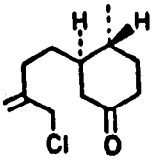

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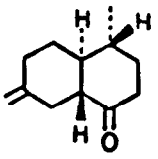

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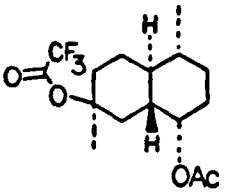

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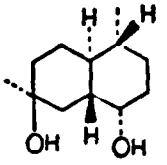

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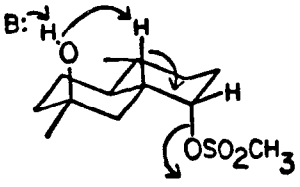

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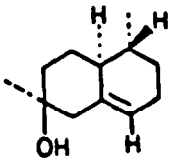

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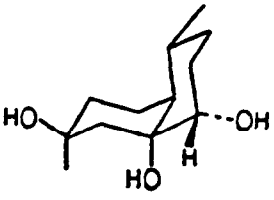

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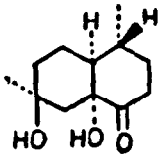

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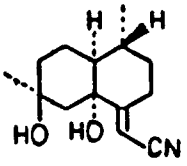

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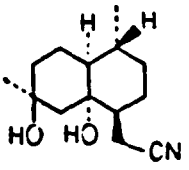

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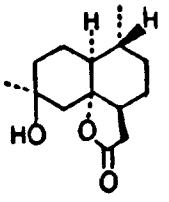

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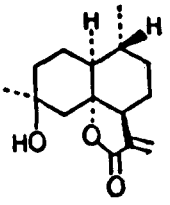

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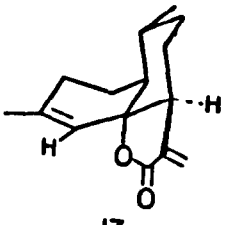

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axial trifluoroacetate 7 (smaller "A" value) and, accordingly, lithium aluminum hydride reduction of 7 gave an 8:1 mixture favoring diol 8[5] (80% from 6), mp 107-8°. We had planned[7] that intramolecular alkoxide-induced elimination of the derived mesylate 9 (one eq. MsCl, pyridine with 8) would assure regioselective formation of 10 (potassium t-butoxide/t-BuOH-THF, 4h, 25°) and were pleased to achieve the desired outcome (92% yield). ^{13}C NMR verified that only one alkene had been produced.[8] Stoichiometric osmylation[9] of 10 led to triol 11,[5] mp 110-2°, as indicated by the equatorial secondary carbinol proton (δ3.65, t, J=2). Swern oxidation[10] of 11 (oxalyl chloride, DMSO, triethylamine, -78°) was followed by immediate Wadsworth-Emmons addition of dimethyl cyanomethylphosphonate to keto-diol 12[5] ($\nu_{C=O}$ 1708 cm^{-1}), resulting in 70% yield of α,β-unsaturated nitrile 13,[5] mp 54-6° (ca. 10:1 isomer ratio). Lithium aluminum hydride reduction[3] of 13 gave the saturated, oily diol-nitrile 14[5] in 75% yield. Hydrolysis (KOH/isopropyl alcohol-water reflux), followed by lactonization (p-tosyl chloride/pyridine, 24 h, 40°) afforded the hydroxy-lactone 15[5] (IR ($CHCl_3$): 3600, 1775 cm^{-1}), mp 120-2°, in 55% overall yield from 14. Treatment of 15 with excess lithium diisopropylamide (10 eqs.), followed by carboxylation, led to crude α-carboxylactone which was immediately reacted with N,N-dimethylmethyleneammonium iodide (Eschenmoser's salt) to produce α-methylene-γ-lactone 16[5] (95% yield), mp 137.5-138.5°.

Thionyl chloride-induced dehydration of 16 gave the desired unsaturated lactone 17 (vinyl singlet at δ 5.04), along with unseparable isomeric alkenes (δ 5.28 and δ 4.59, 4.61). The undesired impurities were only removable by preferential epoxidation (MCPBA/K_2CO_3, 1:1 CH_2Cl_2-hexane, 0°, 24 h) and chromatographic separation of the resultant epoxides. The remaining pure 17[5] was again epoxidized (48 hrs., K_2CO_3 buffer required), yielding a ~1:1 mixture of arteannuin B (1) and epi-arteannuin B. Florosil chromatography afforded pure (±)-1, mp 139-141°, which was shown to be identical with natural (-)-1 by TLC, IR, MS (EI and FAB), 90 and 300 mHz ^1H NMR.

Acknowledgments: We are grateful to the National Science Foundation (Grant CHE-8026526) and to Merck, Sharp and Dohme Research Laboratories for financial support. In addition we thank Mr. Ben-xin Zhi, Dr. Joseph P. Vacca and Dr. Philip G. Marsh for technical assistance, and also Professor Stefanovic (Belgrade) and Dr. Daniel Klayman (Walter Reed Army Institute of Research, Washington, D.C.) for samples of natural arteannuin B.

References and Footnotes

1. a) Initial isolation: D. Jeremic, A. Jokic, A. Behbud and M. Stefanovic, Tetrahedron Lett., 3039 (1973).
   b) X-ray structure determination: M. R. Uskokovic, T. H. Williams and J. F. Blount, Helv. Chim. Acta., 57, 600 (1974); D. G. Leppard, M. Rey, A. S. Dreiding and R. Grieb, Helv. Chim. Acta., 57, 602 (1974).

2. O. Goldberg, I. Deja, M. Rey and A. S. Dreiding, Helv. Chim. Acta., 63, 2455 (1980). These workers prepared three stereoisomers of (±)-arteanniun B, all having cis-fused γ-lactone rings.

3. P. T. Lansbury and J. P. Vacca, Tetrahedron Lett., 23, 2623 (1982).

4. M. G. Silvestri, J. Org. Chem., 48, 2419 (1983). The availability of (+)-R-4-methyl-2-cyclohexenone, from (+)-pulegone, means that our synthesis can lead to (-)-1, using this chiral starting material.

5. All new compounds were characterized by an appropriate combination of infrared, ^{1}H and ^{13}C NMR and mass spectroscopy (EI or CI); elemental compositions were determined by combustion analysis (C,H) or HRMS.
In addition to spectral data cited in the text, salient information for other compounds is given below:
5: IR(film) 1715, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.62 (s,2H), 0.98 (d,J=6Hz,3H)

6: IR(film) 1740, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.85 (m,1H), 4.52 (s,2H), 1.98 (s,3H), 0.86 (br s,3H).

13: IR(CH_2Cl_2) 3590, 2200, 1615 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.57 (d,J=1Hz,1H), 0.95 (d,J=6Hz,3H).

16: IR(CCl_4) 3630, 1780, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.06 (d,J=3.2Hz,1H), 5.34 (d,J=3.2Hz,1H), 2.65 (m,1H), 0.98 (d,J=6 Hz,3H).

17: IR($CHCl_3$) 1780, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.03 (d,J=3.2 Hz,1H), 5.28(d,J=3.2Hz, 1H), 5.04 (s,1H), 0.95 (d,J=6 Hz,3H).

6. K. B. Sharpless and B. Chabaud, J. Org. Chem., 44, 4204 (1979).

7. F. M. Menger, J. F. Chow, H. Kaiserman and P. L. Vasquez, J. Am. Chem. Soc., 105, 4996 (1983).

8. Vinyl carbon signals at 137.1(s) and 123.9(d) ppm; in contrast, the tertiary carbinol epimer of 8 was eliminated much slower than 9 and gave the expected E2 alkene, with vinyl carbon doublets at 126.6 and 132.1 ppm.

9. Ample precedent existed for preferential osmylation on the side of the double bond anti- to the hydroxyl group, cf. J. K. Cha, W. J. Christ and Y. Kishi, Tetrahedron Lett., 24, 3943, 3947 (1983).

10. D. Swern, Synthesis, 165 (1981).

(Received in USA 30 May 1986)