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BORONTRIFLUORIDE CATALYZED CYCLIZATION OF COSTUNOLIDE.

SYNTHESIS OF 4α-HYDROXYCYCLOCOSTUNOLIDE

Tikam C. Jain and J. Edmund McCloskey

Department of Chemistry, University of Victoria
Victoria, British Columbia, Canada.

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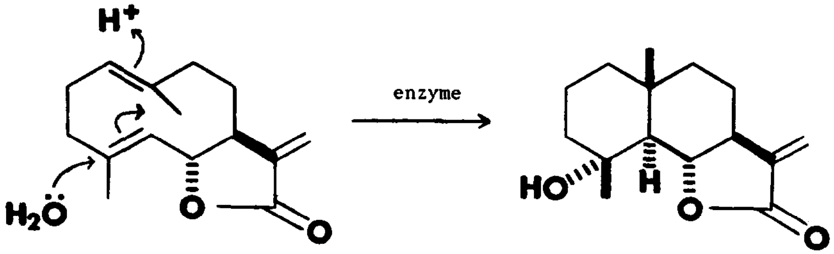
As a part of our research program directed toward the synthesis of biogenetically feasible natural products,[1,2] it was envisioned that enzyme catalyzed cyclization of a precursor such as (I) in nature could result in the formation of a C-4 oxygenated sesquiterpene lactone (II)* where the overall process involves stereospecific addition of a water molecule. Consequently, early in 1969 we undertook the transformation of costunolide (I) to 4α-hydroxycyclocostunolide (II) anticipating that some day 4α-hydroxycyclocostunolide (II) would turn out to be a natural product. After several unsuccessful attempts, we have been able to accomplish the conversion of costunolide (I) to 4α-hydroxycyclocostunolide (II) which is disclosed in this communication, further prompted by a recent report[5] on the isolation of vaseyanin** from *Artemisia tridentata* SSP. *vaseyana*.



I

II

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* The assignment of stereochemistry implicit in (II) is based on our carbocyclization studies of costunolide and related substrates.[3,4]

** The structure (II) has been assigned to vaseyanin; however, to the best of our knowledge neither the physical constants nor the structural evidence for vaseyanin have been so far published by Bhadane and Shafizadeh.

Treatment of costunolide (I) with BF_3-Et_2O at room temperature for 1-10 minutes afforded a viscous product showing three spots on TLC plate. The infrared and N.M.R. spectra of the crude reaction product, besides possessing relevant features for cyclocostunolides (III and IV), displayed a band at 3605 cm^{-1} with a sharp singlet at 8.67 τ* expected of a C-4 hydroxylated methyl unit in (II). By proper combination of column chromatography over silver nitrate impregnated silica gel and preparative TLC, the crude mixture was resolved into exo- and endo-cyclocostunolides (III and IV) and 4α-hydroxycyclocostunolide (II) in overall 28, 37 and 1.5% yields**, respectively. The two isomers of cyclocostunolides*** (III and IV) were unambiguously identified by mixed melting point, specific rotation and infrared spectral comparisons with authentic samples[1]. Although the spectral features of TLC pure 4α-hydroxycyclocostunolide (II) were compatible with its structure, the small quantity of it did not permit us to confirm the assignment of stereochemistry portrayed in (II). This was eventually accomplished by an independent synthesis described in the sequel.

When stirred with N-bromosuccinimide (NBS) in aqueous acetone at room temperature for 46 hours, costunolide amine adduct[3] (V) furnished a mixture of bromolactones (VI) and bromohydrin (VII), established by their characteristic features in the infrared and N.M.R. spectra of the crude reaction product. Rapid column chromatography of the mixture over basic alumina (grade IV) led to the isolation of the desired bromohydrin (VII) as a foam [m.p. 44-50°, $[\alpha]_D^{28}$ + 12.3° (c, 1.47); ν_{max}^{KBr}: 3595 and 1776 cm^{-1}]. Further attempts to purify bromohydrin (VII) were thwarted by its instability, thus subsequent operations were performed on this material**** which analyzed for $C_{17}H_{28}O_3NBr$ by high resolution mass spectrometry. Moreover, the N.M.R. signal at 8.88 τ attributed to the angular methyl

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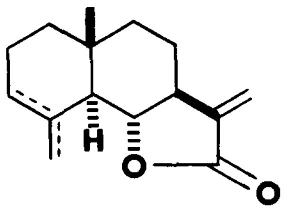
* In addition, the angular methyls of (II, IV and III) appeared as distinct singlets at 9.01, 9.11 and 9.17 τ, respectively.

** Based on the weights of TLC pure fractions isolated.

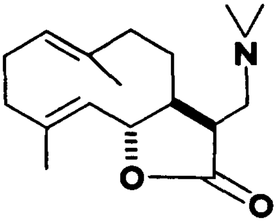
*** α-Cyclocostunolide (IV) and C-11 dihydroderivative of β-cyclocostunolide (III) have been recently isolated[6] from the Brazilian plant *Mochina vellutina*.

**** The presence of an isomeric impurity in small proportion was evident by the infrared band at 1730 cm^{-1}; however, this was removed during purification of the final product.

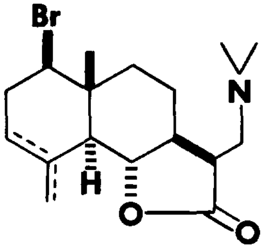


III, exo-isomer

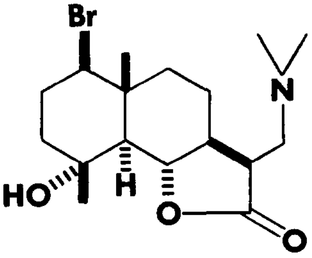
IV, endo-isomer



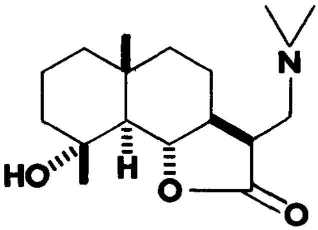
V



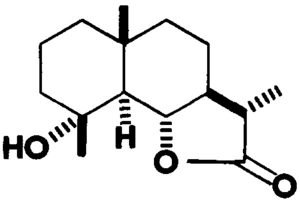
VI



VII



VIII



IX

at C-10 in (VII) was paramagnetically displaced by 0.13 p.p.m. relative to C-10 methyl of the debromo compound (VIII, 9.01 τ) produced by the catalytic hydrogenation (Pd-C; 10%) of (VII) in ethanol containing a few drops of triethylamine. Upon treatment with 5% aq. $NaHCO_3$ at room temperature for 1 hour, the methiodide of (VIII) furnished a product containing (II) which upon chromatography over silica gel column followed by crystallizations from pet. ether-ether yielded 4α-hydroxycyclocostunolide (II) [m.p. 69-71°, $[\alpha]_D^{26}$ + 29.9° (c, 0.84)] analyzed for $C_{15}H_{22}O_3$, further supported by accurate mass measurements [$C_{15}H_{22}O_3$: observed mass 250.1564, calculated mass 250.1569].

The final proof of the structure of 4α-hydroxycyclocostunolide (II) [ν_{max}^{KBr}: 3605 (hydroxyl), 1765, 1665 and 870 cm^{-1} (α,β-unsaturated α-methylene γ-lactone); u.v. spectrum: λ_{max}^{EtOH} 213 nm (ε 6071); mass spectrum m/e (%Σ_{18}): 250 (0.31, molecular ion), 235 (7.30, $M-CH_3$), 217 (2.3, $M-CH_3 + H_2O$); N.M.R. spectrum ($CDCl_3$) τ: 3.89, 4.55 (doublets, J=3.0Hz, 1H each, $>C=CH_2$ next to $>C=O$), 5.95 (q, 1H, C-6 hydrogen), 7.32 (broad, hydroxyl, disappeared after D_2O exchange), 8.67 (s, 3H, C-4 methyl) and 9.03 (s, 3H, C-10 methyl)]* was provided by its catalytic hydrogenation (PtO_2-EtOH) to dihydro derivative identical with an authentic specimen of 4α-hydroxycyclodihydrocostunolide (IX) by mixed melting point, infrared and N.M.R. spectral comparisons. This chemical correlation with (IX), a compound with well-proven stereostructure[7], establishes unequivocally the stereostructure of 4α-hydroxycyclocostunolide portrayed in (II). Finally, the spectral comparisons of (II) obtained by two different routes confirmed their identity.

Acknowledgments

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REFERENCES

1. T. C. Jain and J. E. McCloskey, Tetrahedron Letters, 2917 (1969).
2. T. C. Jain and J. E. McCloskey, Tetrahedron Letters, 4525 (1969).
3. T. C. Jain, C. M. Banks and J. E. McCloskey, Tetrahedron Letters, 2387 (1970).
4. For a comprehensive account see, C. M. Banks, Ph.D. Dissertation, University of Victoria, 1970; forthcoming Ph.D. Dissertation of J. E. McCloskey, University of Victoria.
5. N. R. Bhadane and F. Shafizadeh, Abstracts of Papers, No. 60, p. 54, 25th Annual Northwest Regional Meeting of the American Chemical Society, June 17-19, 1970.
6. T. Tomassini, personal communication, August 20, 1970.
7. T. C. Jain, C. M. Banks and J. E. McCloskey, Experientia, **25**, 906 (1969).

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* N.M.R. spectra were obtained with Varian Associates HA-60 and Perkin-Elmer-R-12A spectrometers using TMS as internal standard. Specific rotations were determined in $CHCl_3$ solution on a Perkin-Elmer model 141 polarimeter.