Pergamon

Tetrahedron Letters, Vol. 38, No. 51, pp. 8815-8818, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10507-X

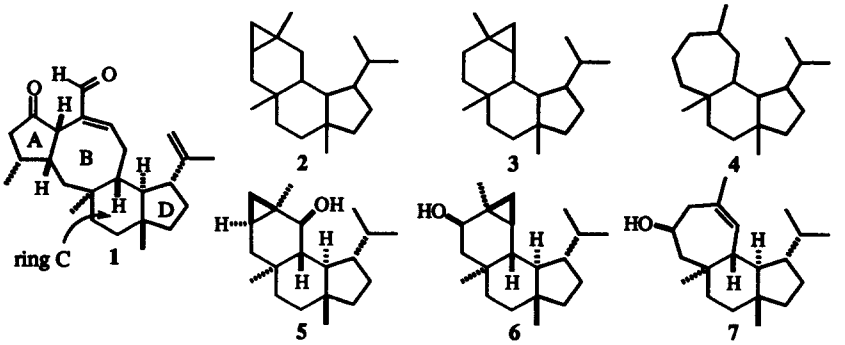
Total Syntheses of the Diterpenoids (±)-Verrucosan-2β-ol, (±)-Neoverrucosan-5β-ol, and (±)-Homoverrucosan-5β-ol. An Approach to the Synthesis of the Sesterterpenoid Variecolin

Edward Piers* and Serge L. Boulet

Department of Chemistry, University of British Columbia
2036 Main Mall, Vancouver, British Columbia, Canada V6T 1Z1

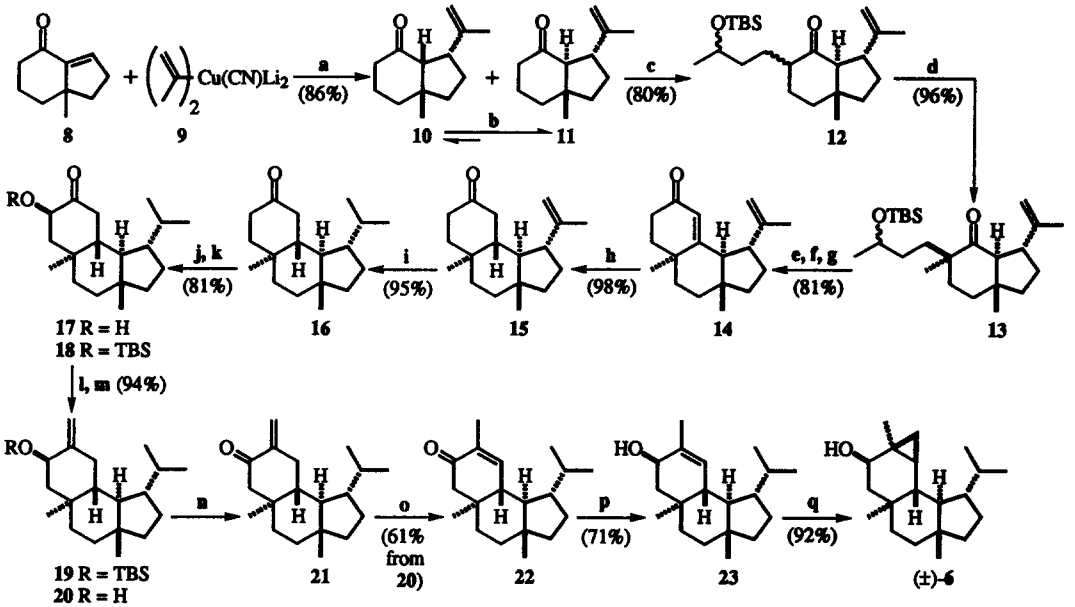
Abstract: Efficient total syntheses of the racemic versions of the diterpenoids verrucosan-2β-ol (**5**), neoverrucosan-5β-ol (**6**), and homoverrucosan-5β-ol (**7**) are described. The production of the key intermediate **15** suggests a possible synthetic approach to the tetracyclic natural product variecolin (**1**). © 1997 Elsevier Science Ltd.

The sesterterpenoid (-)-variecolin, produced by fermentation of the fungus *Aspergillus variecolor* MF138, was shown[1] to possess the constitution and relative configuration depicted in formula **1**. This architecturally novel substance is an angiotensin II receptor binding inhibitor and, thus, **1** (or structurally related analogs) may be of use in the treatment of hypertension.[1] The structure of the functionalized CD-ring portion of **1** is closely related to that of the substituted bicyclo[4.3.0]nonane segment of the verrucosane, neoverrucosane, and homoverrucosane families of diterpenoids, which possess the carbon skeletons shown in **2**, **3**, and **4**, respectively.[2] (-)-Verrucosan-2β-ol (**5**)[3], (-)-neoverrucosan-5β-ol (**6**)[4], and (+)-homoverrucosan-5β-ol (**7**),[4b,c] which possess the absolute configurations shown in the structural formulas, are, respectively, members of these relatively small groups of natural products. In connection with developing a viable approach to the synthesis of **1**, we report herein total syntheses of the racemic versions of **5**, **6**, and **7**. To our knowledge, this work represents the first reported synthesis of a verrucosane, neoverrucosane, or homoverrucosane diterpenoid.



The synthesis of (±)-neoverrucosan-5β-ol (**6**) is outlined in Scheme 1. Me_3SiCl–facilitated[5] conjugate addition of the higher order cuprate **9**[6] to the known[9] bicyclic enone **8** provided a mixture of the epimers **10**[10] and

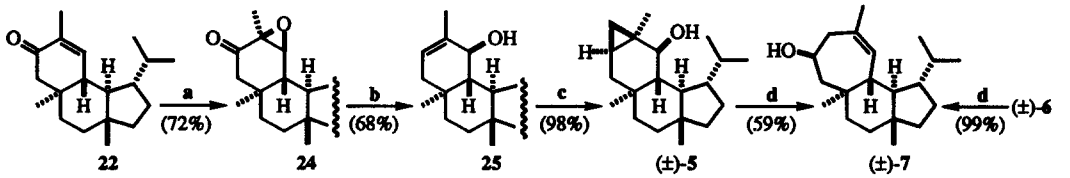
11, in a ratio of approximately 11:1. Thus, with respect to the new stereogenic center generated β to the carbonyl group of **8**, this 1,4–addition is completely stereoselective.[11] Equilibration (step **b**, Scheme 1) of the mixture of **10** and **11** provided (95%) a mixture of the same two compounds, in a ratio of 1:14.[11,12] Separation of these substances by flash chromatography on silica gel[13] provided pure **11** (~65%)[14] and, thus, an intermediate with the correct relative configuration at three of the stereogenic centers present in **6** was readily synthesized.



Scheme 1. **a:** Me_3SiCl, THF, –78 °C; NH_4Cl, H_2O. **b:** MeONa, MeOH, 40 °C. **c:** $(Me_3Si)_2NK$, THF, –78 °C; 2-(*tert*-butyldimethylsilyloxy)-4-iodobutane, HMPA, –78 °C to –48 °C to r.t. **d:** *i*-Pr_2NLi, THF, –78 °C to 0 °C; MeI (excess), –78 °C to r.t. **e:** Bu_4NF, THF, r.t. **f:** pyridinium chlorochromate, Celite, CH_2Cl_2, r.t. **g:** EtONa, EtOH, reflux. **h:** Li, NH_3, *t*-BuOH, THF, –78 °C; NH_4Cl (solid). **i:** H_2 (1 atmosphere), Pt, EtOAc, r.t. **j:** $(Me_3Si)_2NK$, THF, –78 °C to 0 °C; dimethyldioxirane, acetone, –78 °C. **k:** Me_2(*t*-Bu)SiCl, imidazole, CH_2Cl_2, r.t. **l:** $Cp_2TiCH_2AlClMe_2$ (Tebbe reagent), benzene, THF, r.t. **m:** Bu_4NF, THF, r.t. **n:** Pr_4NRuO_4, *N*-methylmorpholine-*N*-oxide, 4Å molecular sieves, CH_2Cl_2, r.t. **o:** $RhCl_3 \cdot 3H_2O$, EtOH, reflux. **p:** $NaBH_4$, $CeCl_3 \cdot 6H_2O$, MeOH, r.t. **q:** Et_2Zn, ICH_2Cl, $ClCH_2CH_2Cl$, 0 °C.

Alkylation of the potassium enolate of **11** with 2-(*tert*-butyldimethylsilyloxy)-4-iodobutane,[15] followed by methylation of the resultant product **12** (a mixture of four diastereomers), provided, in excellent overall yield, the ketone **13**. The fact that the latter substance consisted of only two diastereomers showed clearly that the methylation step had occurred with very high stereoselectivity. The expectation[17] that the methyl group had been installed in an axial orientation was verified by suitable proton NMR nuclear Overhauser enhancement difference (NOED) experiments and by the eventual acquisition of (±)-**6**. Suitable functional group interconversions transformed **13** into the corresponding dione (a *single* diastereomer), which, upon subjection to base–promoted ring closure, was converted into the tricyclic enone **14**. Metal-ammonia reduction of **14** produced the ketone **15**, which should serve as a suitable intermediate for the total synthesis of variecolin (**1**).[18] For the present work, the

isopropenyl group in **15** was hydrogenated and the acquired ketone **16** was sequentially treated with base and dimethyldioxirane[19] to give the α-hydroxylated product **17** as a single diastereomer. Proton NMR NOED experiments showed that the carbinol proton in **17** is 1,3-diaxial to the angular Me group associated with the cyclohexanone ring. Conversion of **17** into the *tert*-butyldimethylsilyl ether **18**, followed by methylenation of the latter substance with the Tebbe reagent,[20] and subsequent fluoride–mediated cleavage of the silyl ether linkage in **19**, afforded the allylic alcohol **20** in very high overall yield. All attempts to effect isomerization of the exocyclic double bond in **19** or **20** to the required endocyclic position (see **23**) failed. However, oxidation[21] of **20**, followed immediately by treatment of the resultant enone **21**[22] with $RhCl_3$ in EtOH,[23] provided, in good overall yield, the enone **22**. Reduction[24] of this material furnished, as the major product, the required alcohol **23**,[25] which was stereoselectively cyclopropanated[26] to give (±)-neoverrucosan-5β-ol (**6**).[27]



Scheme 2. **a:** dimethyldioxirane (excess), acetone, CH_2Cl_2, r.t. **b:** H_2NNH_2, 1-hexene, MeOH, HOAc, 0 °C. **c:** Et_2Zn, ICH_2Cl, $ClCH_2CH_2Cl$, 0 °C. **d:** H_2SO_4, H_2O, acetone, reflux.

Scheme 2 summarizes the completion of the syntheses of (±)-verrucosan-2β-ol (**5**) and (±)-homoverrucosan-5β-ol (**7**). Direct epoxidation of the enone **22** with excess dimethyldioxirane[28] provided a single product, **24**, derived from approach of the reagent from the less hindered face of the carbon–carbon double bond. Subjection of **24** to the Wharton reaction,[29] followed by face-selective cyclopropanation[26] of the olefinic bond in the acquired product **25**, provided (±)-verrucosan-2β-ol (**5**).[27] Treatment of either (±)-**5** or (±)-**6** with aqueous H_2SO_4 in acetone[3a,4a] furnished racemic homoverrucosan-5β-ol (**7**).[27]

Cytotoxicity studies on compounds **5**–**7** are underway and the results will be published in due course.

Acknowledgments. We thank NSERC of Canada for financial support and for a Postgraduate Scholarship (to S. L. B.).

References and Notes

1. Hensens, O. D.; Zink, D.; Williamson, J. M.; Lotti, V. J.; Chang, R. S. L.; Goetz, M. A. *J. Org. Chem.* **1991**, *56*, 3399.
2. Toyota, M.; Nakaishi, E.; Asakawa, Y. *Phytochemistry* **1996**, *43*, 1057, and citations therein.
3. (a) Takaoka, D. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2711. (b) Hefter, J.; Richnow, H. H.; Fischer, U.; Trendel, J. M.; Michaelis, W. *J. Gen. Microbiol.* **1993**, *139*, 2757.
4. (a) Matsuo, A.; Nozaki, H.; Nakayama, M.; Takaoka, D.; Hayashi, S. *J. Chem. Soc., Chem. Commun.* **1980**, 822. (b) Wu, C.-L.; Chang, S.-J. *J. Hattori Bot. Lab. No. 64*, **1988**, 151. (c) Compagnone, R. S.; Faulkner, D. J. *J. Nat. Prod.* **1995**, *58*, 145.
5. Nakamura, E. In *Organocopper Reagents, A Practical Approach*, Taylor, R. J. K., Ed. Oxford University Press: Oxford, 1994; Chapter 6.

6. This reagent was prepared[7] by addition of an ethereal solution of isopropenyllithium[8] (2 equiv.) to a suspension of CuCN (1 equiv.) in dry THF (–78 °C, with brief warming to –48 °C, if necessary).
7. Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.
8. Leonard, J.; Ryan, G. *Tetrahedron Lett.* **1987**, *28*, 2525.
9. Bal, S. A.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045.
10. All new compounds reported herein displayed spectra (IR, ^1H and ^{13}C NMR) in accord with assigned structures and gave satisfactory elemental analyses and/or molecular mass determinations (HRMS).
11. Piers, E.; Oballa, R. M. *Tetrahedron Lett.* **1995**, *36*, 5857.
12. *Cf.* Cicero, B. L.; Weisbuch, F.; Dana, G. *J. Org. Chem.* **1981**, *46*, 914.
13. (a) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923. (b) Taber, D. F. *J. Org. Chem.* **1982**, *47*, 1351.
14. Since the chromatographic separation of **10** and **11** was quite difficult, the yield of pure **11** varied somewhat from experiment to experiment. However, mixed fractions could easily be recycled.
15. This material was prepared as follows. Addition of HI to but-3-en-2-one in benzene,[16] followed by immediate reduction (*i*-Bu_2AlH, benzene, 0 °C) of the resultant product, gave 4-iodobutan-2-ol. Treatment (CH_2Cl_2, r.t.) of this alcohol with Me_2(*t*-Bu)SiCl in the presence of imidazole gave the required iodide in 78% overall yield.
16. Stowell, J. C.; King, B. T.; Hauck, H. F., Jr. *J. Org. Chem.* **1983**, *48*, 5381.
17. House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 1000.
18. Studies directed toward the synthesis of **1** are in progress.
19. (a) Guertin, K. R.; Chan, T.-H. *Tetrahedron Lett.* **1991**, *32*, 715. (b) Adam, W.; Prechtl, F. *Chem. Ber.* **1991**, *124*, 2369.
20. (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Pine, S. H.; Shen, G. S.; Hoang, H. *Synthesis* **1991**, 165.
21. Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13.
22. The oxidation reaction mixture was passed through a short column of silica gel (elution with Et_2O), the filtrate was diluted with EtOH, the CH_2Cl_2 and Et_2O were removed under reduced pressure, and $RhCl_3 \cdot 3H_2O$ was added to the resultant ethanol solution of **21**. Not unexpectedly, concentration of solutions of **21** resulted in dimerization of this material.
23. Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 359.
24. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
25. The epimer of **23**, produced in 26% yield, could be separated from **23** by silica gel chromatography.
26. Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974.
27. This material exhibited ^1H and ^{13}C NMR spectra identical with those derived from the natural product. We are very grateful to Professor Takaoka for copies of the ^1H and ^{13}C NMR spectra of compounds **5**–**7**, to Professor Faulkner for samples of **6** and **7**, and to Professors Faulkner and Wu for copies of the ^1H and ^{13}C NMR spectra of **6** and **7**.
28. Adam, W.; Hadjiarapoglou, L.; Smerz, A. *Chem. Ber.* **1991**, *124*, 227.
29. Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615.

(*Received in USA* 26 *September* 1997; *accepted* 24 *October* 1997)