Pergamon

Tetrahedron Letters, Vol. 35, No. 13, pp. 2013-2016, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0240-X

Terpenoid Chirons: Preparation and Transformations of 2-Hydroxy-1,1,4a(R),6-Tetramethyl-*Trans*-$\Delta^{5,6}$-Octalin

J. R. Falck*, Sukumar Manna, and S. Chandrasekhar

Departments of Molecular Genetics and Pharmacology
University of Texas Southwestern Medical Center
Dallas, Texas 75235 U. S. A.

L. Alcaraz and C. Mioskowski*

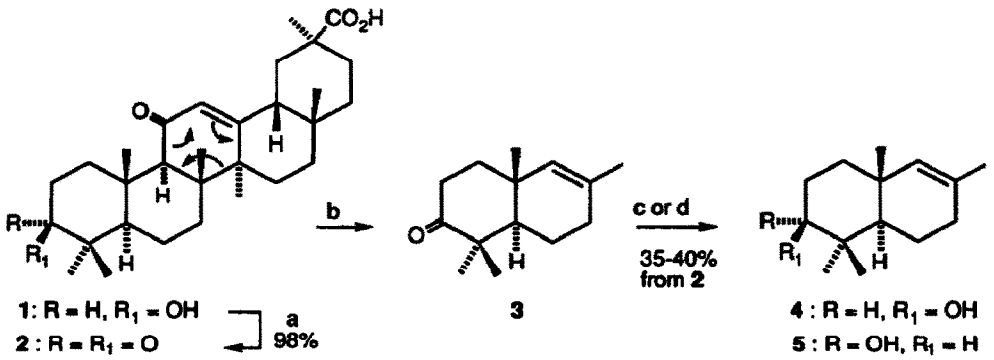
Laboratoire de Chimie Bio-Organique, associé au CNRS
Université Louis Pasteur, Faculté de Pharmacie
67401 Illkirch, France

Key Words: thermolysis, steroid, octahydronaphthalene, retro-Diels-Alder, glycyrrhetinic acid

Abstract: Octalins **4** and **5** are prepared conveniently in 3 steps from commercial 18ß-glycyrrhetinic acid and converted to a variety of functionalized *trans*-AB ring chirons.

In recent years, there has been a worldwide resurgence of interest in the asymmetric total synthesis of sesquiterpenes and higher homologs.[1] This has been sustained in part by the burgeoning list of novel compounds from both marine and terrestrial sources,[2] many of which display significant biological activities. To help contend with the synthetic challenge, we have sought to devise a new generation[3] of optically active terpenoid building blocks or chirons by excision of appropriate subunits from a readily available but little utilized segment of the chiral pool, i.e., steroids.[4] Herein, we describe a convenient, multi-gram synthesis of 2α– and 2β-hydroxy-1,1,4a(R),6-tetramethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalenes **4** and **5**, respectively, and their conversion to a variety of useful AB-ring chirons.

SCHEME 1



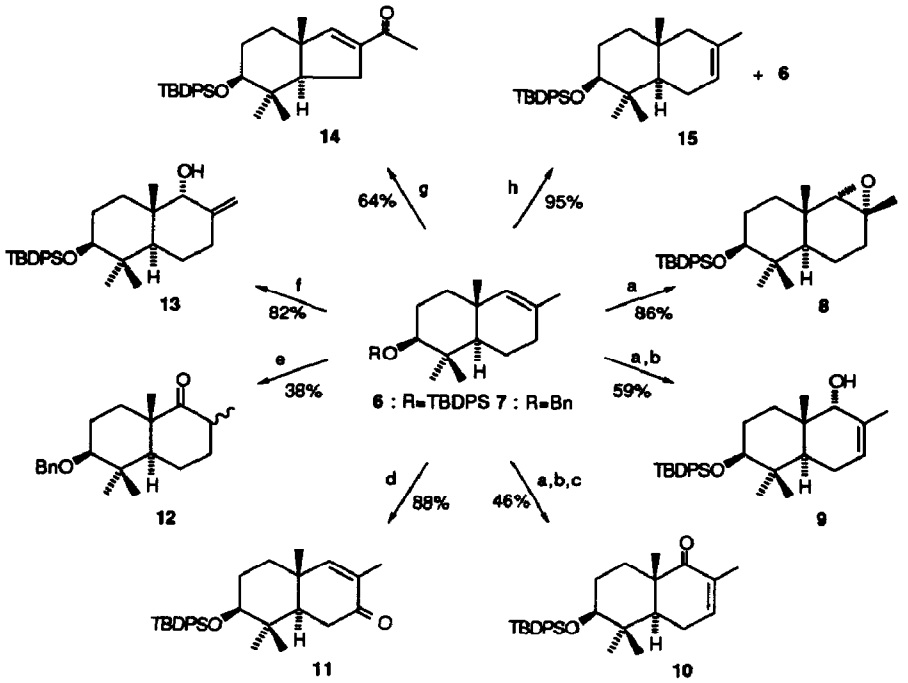
[a] CrO_3/H_2SO_4, acetone, 0°C, 1 h. [b] BMPS, 350°C, 40 mmHg, 3 h. [c] $NaBH_4$, MeOH, -78 to 0°C, 1 h. [d] $KB[CH(CH_3)C_2H_5]_3H$, THF, 0°C, 1 h.

Initially, the key octalone intermediate **3**[5,6] was obtained in poor yield by simple thermolysis of ketone **2**, which

in turn was derived from commercial 18ß-glycyrrhetinic acid 1[7] by Jones oxidation (Scheme 1). However, after extensive optimization studies, preparatively useful amounts of **3** could be generated by mixing **2** with the antioxidant 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (BMPS) (10% w/w) and distillation from a kugelrohr or bulb-to-bulb apparatus under reduced pressure. This degradation can be envisioned as a retro-Diels-Alder reaction,[8] but is more likely a heterolytic process.[9]

Sodium borohydride reduction of the crude pyrolysate **3** led stereoselectively to ß-alcohol **4** in 35-40% overall yield from **2**. On the other hand, the α-alcohol **5** was the sole product using potassium tri-*sec*-butylborohydride (K-Selectride®). The sequence of thermolysis and hydride reduction using 40 mmoles of **2** consistently furnished over 3 g of **4** or **5**. Expensive pyrolysis equipment or high-temperature ovens were not required even on a preparative scale.

SCHEME 2



[a]3-$ClC_6H_4CO_3H$, $NaHCO_3$, CH_2Cl_2, 0°C, 0.5 h. [b]BF_3•Et_2O, THF, 0°C, 2 h. [c]MnO_2 (20 equiv), CH_2Cl_2, 50°C, 24 h. [d]pyridinium dichromate, *t*-BuOOH (90%), Celite, C_6H_6, 12 h. [e](i) BH_3, THF, 23°C, 5 h; H_2O_2/NaOH, 23°C, 4 h; (ii) PCC, CH_2Cl_2, 23°C, 2h. [f]$^1O_2$, C_5H_5N, 23°C, 24 h; $NaBH_4$, MeOH, 0°C, 2 h. [g](i) O_3, MeOH, -15°C, 15 min; $H_2NC(S)NH_2$, 23°C, 1h; (ii) K_2CO_3, MeOH, 23°C, 0.5 h; (iii) MsCl, Et_3N, CH_2Cl_2, 0°C, 10 min; (iv) DBU, CH_2Cl_2, 23°C, 8 h. [h]$RhCl_3$, EtOH, 100°C, 20 h.

The potential utility of **4** and **5** was explored by their conversion to a variety of functionalized AB ring chirons (Scheme 2, shown for **4** only). For this, the C(3)-alcohol was protected as its *tert*-butyldiphenylsilyl (TBDPS) ether **6** (TBDPS-Cl, DMAP, DMF, 50°C, 24 h, 90%) or benzyl ether **7** (Bn-Br, NaH, DMF, 23°C, 3h, 69%). Treatment of **6** with 3-chloroperbenzoic acid gave rise to epoxide **8**, free of any ß-isomer, which

readily rearranged to allylic alcohol **9** upon exposure to BF_3•Et_2O at 0°C. Interestingly, the interaction of **8** with a Bronsted acid, camphorsulfonic acid, resulted in a 1:2 mixture of **9** and **13**. Mild oxidation of **9** afforded enone **10**, mp 123-125°C; its regioisomer **11** was secured by direct oxidation of **6** with pyridinium dichromate/*t*-butyl hydroperoxide.[10] Hydroboration of **7** was relatively sluggish, presumably due to steric hindrance about the tetra-substituted olefin. Subsequent oxidation led to ketone **12** as a 7:3 mixture of methyl isomers in modest overall yield. As anticipated, reaction of **6** with singlet oxygen smoothly generated exocyclic allylic alcohol **13**. Access to the transfused 6,5-bicycle **14** followed from ozonolysis of **6** and aldol condensation of the resultant keto-aldehyde. Using $RhCl_3$,[11] **6** could be isomerized to a 4:1 equilibrium mixture favoring $\Delta^{6,7}$-olefin **15**.

In consideration of their ease of preparation, cost, and differentially functionalized rings, we anticipate these chirons will find many applications in terpene total synthesis.[12]

Acknowledgement: Supported financially by the USPHS NIH (GM31278), the Robert A. Welch Foundation and the CNRS.

Reference and Notes

1. For recent, pertinent examples containing the 1,1,4a-*trans*-trimethylhydronapthalene moiety see, Forskolin (adenylate cyclase stimulant): Colombo, M.I.; Zinczuk, J.; Rùveda, E.A. *Tetrahedron* **1992**, *48*, 963-1037. K-76 (complement inhibitor): Corey, E.J.; Das, J. *J. Am. Chem. Soc.* **1982**, *104*, 5551. Warburganal (insert antifeedant): de Groot, A.; van Beek, T.A. *Rec. Trav. Chim.* **1987**, *106*, 1-18. Stypoldione (anticancer, ichthyotoxic): Mori, K.; Koga, Y. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 391-394. Taxodione (anticancer): Engler, T.A.; Sampath, U.; Naganathan, S.; Velde, D.V.; Takusagawa, F.; Yohannes, D. *J. Org. Chem.* **1989**, *54*, 5712-5727. Stelliferins (anticancer): Tsuda, M.; Ishibashi, M.; Agemi, K.; Sasaki, T.; Kobayashi, J. *Tetrahedron* **1991**, *47*, 2181-2194. Baiyunoside (sweetener): Yamada, H.; Nishizawa, M. *ibid.* **1992**, *48*, 3021-3044. Ambrox® (perfume component): Büchi, G.; Wüest, H. *Helv. Chim. Acta.* **1989**, *72*, 996.
2. Recent reviews: Fraga, B.M. *Nat. Prod. Reports* **1993**, 397-419. Hanson, J.R. *ibid.* **1993**, 159-174.
3. Preceding paper in this series on chiral precursors via steroid degradation: Manna, S.; Yadagiri, P.; Falck, J.R. *J. Chem. Soc., Chem. Comm.* **1987**, 13, 1324-1325.
4. The exploitation of terpenoids and steroids as chirons has been reviewed: Ho, T.-L. *Enantioselective Synthesis, Natural Products from Chiral Terpenes*; John Wiley and Sons, Inc.: New York, 1992.
5. Satisfactory spectral data (^1H ($CDCl_3$, 250 MHz) and ^{13}C NMR ($CDCl_3$, 62.5 MHz), MS) were obtained for all new compounds using chromatographically homogeneous samples. All specific rotations were performed in $CHCl_3$.
6. Physical and spectral data for **3**: ^1H NMR: δ 5.09 (br s, 1H), 2.35-2.60 (m, 2H), 1.85-2.05 (m, 2H), 1.45-1.70 (m, 5H), 1.60 (s, 3H), 1.08(s, 3H) 1.04 (s, 3H), 0.95 (s, 3H); ^{13}C NMR: δ 217.6, 132.9, 131.1, 50.0, 47.0, 37.5, 34.68, 34.66, 31.3, 26.6, 23.2, 21.0, 20.8, 20.1; MS (CI, CH_4) m/z (rel intensity) 207 (M^++1, 80), 189 (100); $[\alpha]_D^{23}$: +106 (c 0.67); **4**: ^1H NMR: δ 4.92 (app q, J=2.8 Hz, 1H), 3.13 (dd, J=5.1, 10.8 Hz, 1H), 1.81-1.92 (m, 2H), 1.15-1.61 (m, 7H), 1.49 (br s, 3H), 0.90 (s, 3H), 0.81 (s, 3H), 0.69 (s, 3H); ^{13}C NMR: δ 134.9, 131.8, 79.3, 50.1, 38.5, 38.5, 37.8, 34.9, 31.9, 27.9, 23.1, 21.6, 19.3, 15.2; MS (CI, CH_4) m/z (%) 208 (M^+, 12), 191 (100), 175 (24); $[\alpha]_D^{23}$: +32 (c 0.65); *p*-nitrobenzoate of **4** mp: 116-118°C (EtOH); **5**: ^1H NMR: δ 5.08 (q, 1H, J=1.4 Hz), 3.45 (t, 1H, J=2.8 Hz), 1.83-2.10 (m, 2H), 1.58 (d, 3H, J=1.3 Hz), 1.20-1.75 (m, 7H), 0.96 (s, 3H), 0.92 (s, 3H), 0.85

(s, 3H); ^{13}C NMR: δ 135.4, 129.7, 50.8, 44.3, 37.3, 35.0, 32.8, 31.9, 27.8, 25.8, 23.1, 21.8, 21.4, 18.6; **6**: ^{1}H NMR: δ 7.60-7.78 (m, 4H), 7.35-7.50 (m, 6H), 4.95 (d, 1H, J=1.4 Hz), 3.27 (dd, 1H, J=4.6, 11.6 Hz), 1.80-1.95 (m, 2H), 1.61-1.75 (m, 2H), 1.52 (br s, 3H), 1.10-1.51 (m, 5H), 1.05 (s, 9H), 0.96 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H); ^{13}C NMR: δ 136.0, 135.4, 135.0, 134.1, 130.1, 129.4, 129.23, 127.4, 127.2, 81.3, 50.1, 39.4, 37.6, 34.7, 31.8, 28.3, 28.2, 27.1, 23.0, 21.5, 19.6, 18.9, 16.1; MS (CI, CH_4) m/z (%): 447(4), 390 (24), 389 (96), 199 (100); $[\alpha]_D^{23}$: +7.1 (c 0.73); **9**: ^{1}H NMR: δ 7.69-7.80 (m, 4H), 7.28-7.49 (m, 6H), 5.45-5.53 (m, 1H), 3.35 (dd, 1H, J=4.2 and 10.8 Hz), 3.01 (d, 1H, J=6.9 Hz), 1.80-2.08 (m, 2H), 1.78 (br s, 3H), 1.11-1.70 (m, 4H), 1.10 (s, 9H), 0.98 (s, 3H), 0.94 (s, 3H), 0.78 (s, 3H); ^{13}C NMR: δ 135.9, 135.5, 134.0, 133.5, 129.5, 129.3, 127.5, 127.2, 124.9, 81.0, 78.7, 40.2, 39.2, 31.7, 28.1, 27.3, 27.1, 23.8, 21.8, 19.6, 18.6, 16.1; MS (CI, CH_4) m/z (%) 463 (M^++1, 4), 462 (M^+, 6), 405 (100), 385 (78), 199 (88); $[\alpha]_D^{23}$: -44 (c 1.34); **10**: ^{1}H NMR: δ 7.61-7.70 (m, 4H), 7.30-7.42 (m, 6H), 6.61 (br s, 1H), 3.21 (dd, 1H, J=4.4 and 11.1 Hz), 2.30 (dd, 2H, J=8.30 and ~2Hz), 1.67 (app d, 3H, J~2Hz), 1.40-1.64 (m, 5H), 1.08 (s, 3H), 1.05 (s, 9H), 0.99 (s, 3H), 0.96 (s, 3H); ^{13}C NMR: δ 204.9, 143.5, 135.9, 135.0, 133.7, 132.9, 129.6, 129.4, 127.5, 127.3, 80.2, 48.4, 44.4, 39.9, 31.4, 27.7, 27.1, 24.2, 19.5, 17.2, 16.6, 16.2; $[\alpha]_D^{23}$: -11,9 (c 0.91); MS (CI, CH_4) m/z (%) 461 (M^++1, 20), 403 (88), 199 (100); **11**: ^{1}H NMR: δ 7.62-7.79 (m, 4H), 7.38-7.50 (m, 6H), 6.25 (d, 1H, J=1.3 Hz), 3.28 (dd, 1H, J=4.1 and 11.3 Hz), 2.45 (dd, 1H, J=4.8 and 17.4 Hz), 2.34 (dd, 1H, J=12.9 and 17.4 Hz), 1.65 (d, 3H, J=1.2 Hz), 1.04 (s, 9H, 1.02 (s, 3H), 1.01 (s, 3H), 0.90 (s, 3H); ^{13}C NMR: δ 201.1, 157.1, 135.9, 135.0, 133.6, 131.2, 129.6, 129.4, 127.5, 127.3, 80.1, 49.1, 39.2, 36.5, 36.4, 35.1, 27.7, 27.6, 27.0, 19.5, 18.5, 15.7, 15.4; $[\alpha]_D^{23}$: -47 (c 2.4); **14**: ^{1}H NMR: δ 7.65-7.73 (m, 4H), 7.33-7.45 (m, 6H), 6.53 (br s, 1H), 3.31 (dd, 1H, J=4.5 and 11.4 Hz), 2.20-2.39 (m, 2H), 2.22 (s, 3H), 1.15-1.85 (m, 5H), 1.07 (s, 3H), 1.05 (s, 9H), 0.93 (s, 3H), 0.91 (s, 3H). ^{13}C NMR: 197.5, 154.4, 144.4, 136.0, 135.1, 133.9, 129.5, 129.3, 127.5, 127.2, 81.3, 56.3, 47.1, 38.83, 33.9, 28.9, 28.8, 27.4, 27.1, 25.9, 19.6, 18.0, 16.3.

7. Available from Aldrich Chem. Co. or can be prepared from inexpensive glycyrrhizic acid (licorice root) by hydrolysis: Ruzicka, L.; Leuenberger, H. *Helv. Chim. Acta* **1936**, *19*, 1402-1406.
8. Electrocyclic reactions of this type in pentacyclic triterpenes has precedent: Djerassi, C.; Budzikiewicz, H.; Wilson, J.M. *Tetrahedron Lett.* **1962**, 263-270.
9. Ichihara, A: *Synthesis*, **1987**, 207-222.
10. Chidambaram, N.; Chandrasekaran, S. *J. Org. Chem.* **1987**, *52*, 5048-5051.
11. Grieco, P.A.; Nishizawa, M.; Marinovic, N.; Ehmann, W.J. *J. Am. Chem. Soc.* **1976**, *98*, 7102-7104.
12. Falck, J.R.; Chandrasekhar, S.; Manna, S.; Chiu, C.-C.S.; Mioskowski, C.; Wetzel, I. *J. Am. Chem. Soc.* **1993**, *115*, 11606-11607.

(*Received in France* 23 *November* 1993; *accepted* 31 *January* 1994)