Enantioselective Total Synthesis of Oleanolic Acid, Erythrodiol, β-Amyrin, and Other Pentacyclic Triterpenes from a Common Intermediate

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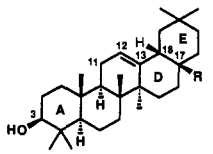
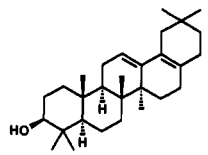
Reported herein is the first enantioselective total synthesis of pentacyclic triterpenes[1] in the oleanane series, including the principal members β-amyrin (**1**), erythrodiol (**2**), and oleanolic acid (**3**), via the key intermediate aegiceradienol (**4**), itself a natural product.[2] Previous research on the synthesis of β-amyrins includes a recently described synthesis of (±)-β-amyrin,[3] the (±)-$\Delta^{13,18}$-isomer of β-amyrin,[4a] and (±)-3-desoxy-11,18-dehydro-β-amyrin.[4b,5] The pathway, reagents, and conditions of our synthesis are summarized in Schemes I and II.



1 R = CH_3
2 R = CH_2OH
3 R = COOH



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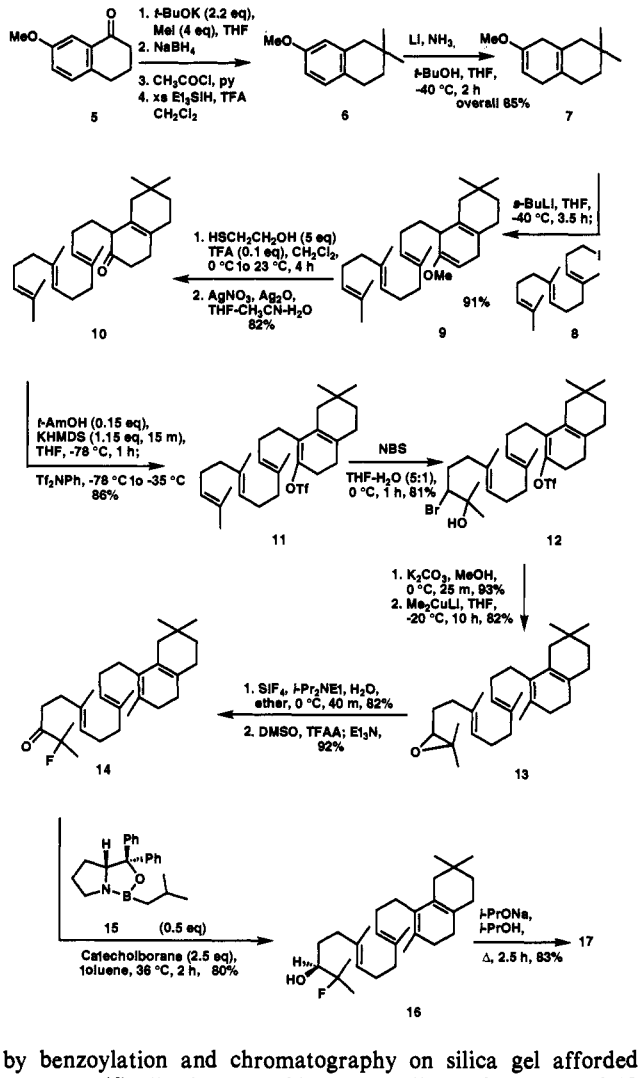
Tetralin **6** (Scheme I) was synthesized from 7-methoxy-1-tetralone (**5**, Aldrich Co.) by dimethylation, carbonyl reduction, acetylation, and reductive cleavage of the benzylic acetate. Birch reduction of **6** gave **7**, which was selectively deprotonated and alkylated with homofarnesyl iodide (**8**)[6] to form **9** in high yield.[7] Direct hydrolysis of **9** to **10** under a variety of acidic conditions was complicated by concomitant formation of the isomeric α,β-enone, and so a two-stage process via the ethylene hemithioketal of **10** was utilized. The vinyl triflate **11** was prepared by alkoxide-promoted selective deprotonation of **10** and reaction with the Hendrickson–McMurry reagent.[8]

Bromohydrin **12** was formed highly selectively by hydroxy bromination of **11**, since the electron-withdrawing triflate substituent deactivates the diene moiety,[9] and converted to the chiral epoxide (*S*)-**17** (92% ee, Daicel AD column) by way of intermediates **13**, **14**, and **16** using recently developed methodology.[10] Cyclization of (*S*)-**17** (Scheme II) with $MeAlCl_2$ followed

Scheme I



by benzoylation and chromatography on silica gel afforded stereospecifically the separable pentacyclic products **18** and **19** (41% total yield, ratio 1.5:1). Additional **18** was obtained from the isomerization of **19** by heating with HCl in acetic acid. Recrystallization of synthetic **18** afforded enantiomerically pure material, mp 225 °C dec, $[\alpha]^{23}_D$ +90° (c = 1, $CHCl_3$), identical in all respects with an authentic sample of aegiceradienol benzoate.[11–13]

Reaction of **18** with the Simmons–Smith reagent resulted in selective methylenation of the 17,18-double bond to give benzoate **20**. The stereochemistry of **20** was demonstrated unequivocally by hydrogenation over Adams Pt catalyst to form δ-amyrin cyclohexanecarboxylate (13,18-double bond isomer of **1** cyclohexanecarboxylate) in 100% yield, identical in all respects with an authentic sample.[13,14] Saponification of this ester afforded δ-amyrin, mp and mixture mp 213–214 °C, $[\alpha]^{23}_D$ −50° (c = 0.3, $CHCl_3$).[13,14] Kharasch free-radical chain oxidation of **21**, the silyl ether corresponding to **20**, resulted in abstraction of hydrogen from C(11) and cyclopropyl cleavage to give the primary benzoate

(1) Sukh Dev, Ed. *Handbook of Terpenoids. Triterpenes, Vols. I and II*; CRC Press: Boca Raton, FL, 1989.
(2) (a) Venkateswara Rao, K.; Bose, P. K. *J. Org. Chem.* **1962**, *27*, 1470. (b) Noller, C. R.; Carson, J. F. *J. Am. Chem. Soc.* **1941**, *63*, 2238.
(3) Johnson, W. S.; Plummer, M. S.; Pulla Reddy, S.; Bartlett, W. R. *J. Am. Chem. Soc.* **1993**, *115*, 515.
(4) (a) van Tamelen, E. E.; Seiler, M. P.; Wierenga, W. *J. Am. Chem. Soc.* **1972**, *94*, 8229. (b) Corey, E. J.; Hess, H.-J.; Proskow, S. *J. Am. Chem. Soc.* **1959**, *81*, 5258; **1963**, *85*, 3979.
(5) Other pentacyclic triterpenes which have been synthesized in racemic form include the following. (a) (±)-Lupeol: Stork, G.; Uyeo, S.; Wakamatsu, T.; Grieco, P.; Labovitz, J. *J. Am. Chem. Soc.* **1971**, *93*, 4945. (b) (±)-Germanicol: Ireland, R. E.; Baldwin, S. W.; Dawson, D. J.; Dawson, M. I.; Dolfini, J. E.; Newbould, J.; Johnson, W. S.; Brown, M.; Crawford, R. J.; Hudrlik, P. F.; Rasmussen, G. H.; Schmiegel, K. K. *J. Am. Chem. Soc.* **1970**, *92*, 5743.
(6) Prepared by homologation of farnesol by the procedure of Corey, E. J.; Jautelat, M. *Tetrahedron Lett.* **1968**, 5787. See also: Dodd, D. S.; Oehlschlager, A. C. *J. Org. Chem.* **1992**, *57*, 2794 and refs cited therein. Kocienski, P.; Wadman, S.; Cooper, K. *J. Org. Chem.* **1989**, *54*, 1215.
(7) This alkylation procedure was far superior to the more conventional enolate alkylation of the ketone corresponding to **7**,which afforded only 40–45% of the desired product **10** in a difficult to separate mixture.
(8) (a) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979. (b) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, 4607.
(9) Compare the preferred meta-bromination of phenyl triflate.
(10) Corey, E. J.; Yi, K. Y.; Matsuda, S. P. T. *Tetrahedron Lett.* **1992**, *33*, 2319.
(11) Prepared from the benzoate of oleanolic acid by oxidative decarboxylation (1.4 equiv of $Pb(OAc)_4$ and 0.5 equiv of $Cu(OAc)_2$ in CH_3CN–pyridine at 80 °C, 72%).
(12) Aegiceradienol (**4**), the 3β-ol corresponding to **18**, was prepared by reaction of **18** with DIBAL in CH_2Cl_2. Synthetic and naturally derived aegiceradienols were identical.
(13) Comparisons for identity included 500 MHz ^1H NMR, ^{13}C NMR, IR, $[\alpha]^{23}_D$, mp, mixture mp, UV, MS, and TLC R_f measurements.
(14) An authentic sample of δ-amyrin was prepared by (1) hydrogenation (H_2, Pt, EtOAc–HOAc) of 3β-acetoxyolean-11,13-diene (Ruzicka, L.; Müller, G.; Schellenberg, H. *Helv. Chim. Acta* **1939**, *22*, 767) and (2) saponification with sodium hydroxide in THF–CH_3OH–H_2O.

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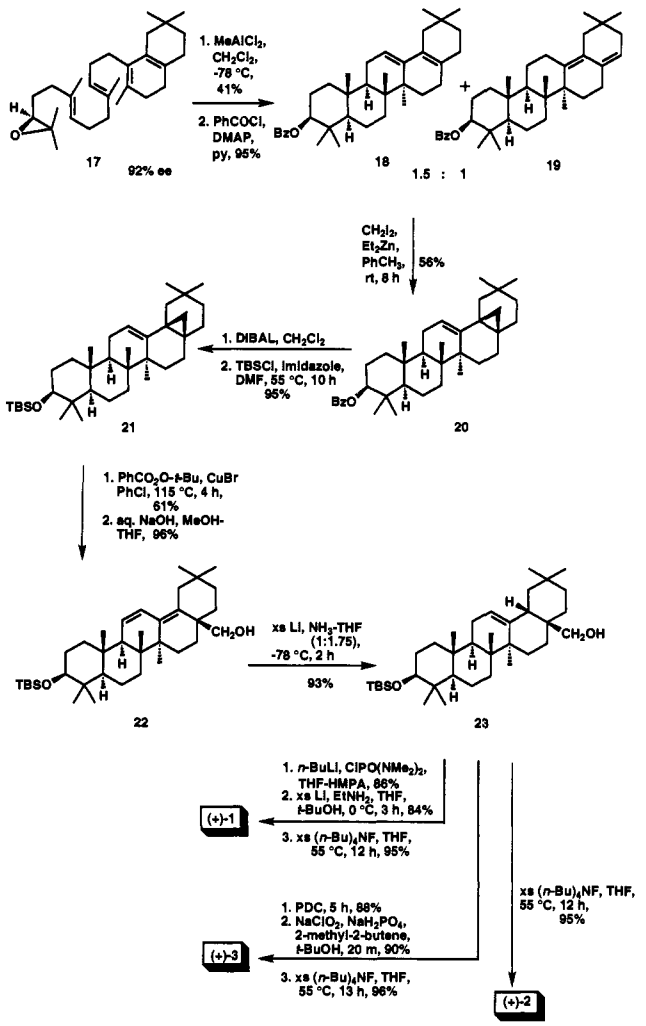
Scheme II



corresponding to **22**, which was converted to **22** by saponification. Reduction of **22** with Li in dry NH_3–THF proceeded as expected for a pathway involving internal proton transfer from the primary hydroxyl to C(18) of an intermediate π-radical anion to form selectively the D/E *cis*-fused product **23**. To our knowledge, this is the first use of this strategy for controlling the stereochemistry and position specificity of a 1,3-diene reduction. Silyl ether **23** was converted to β-amyrin (**1**), mp and mixture mp 194–196 °C, $[\alpha]^{23}_D$ +84° (c = 0.4, $CHCl_3$); erythrodiol (**2**), mp and mixture mp 225–227 °C, $[\alpha]^{23}_D$ +74° (c = 0.4, $CHCl_3$); and oleanolic acid (**3**) and its methyl ester, mp and mixture mp 203-205 °C, $[\alpha]^{23}_D$ +73° (c = 0.9, $CHCl_3$), as shown in Scheme II. In each case, identity of synthetic and authentic samples was confirmed by rigorous comparison.[13]

The total synthesis of triterpenes of the β-amyrin series described above is remarkably short and flexible with regard to providing access to a number of important natural products. A single stereocenter in **17** is used to control the development of the remaining seven stereocenters of **1**–**3** in a manner reminiscent of the biosynthesis of these compounds from (*S*)-2,3-oxidosqualene.[15] In addition to the cyclization of **17** to **18**,[16] there are a number of noteworthy steps in the sequence outlined above which are of quite general interest and utility. The superior efficiency of the conversion of **7** to **9** as compared to more conventional enolate alkylation[7] indicates that the selective formation and alkylation of anions from unsymmetrical 1,4-cyclohexadienes such as **7** can be an advantageous synthetic procedure.[17] The very selective conversion of **11** to bromohydrin **12** demonstrates a new use of the CF_3SO_2O group for the deactivation of olefins toward electrophilic attack. The sequence **12** → **17** illustrates the effectiveness of the chiral oxazaborolidine-catalyzed reduction of ketones[10] in a complex enantioselective synthesis. The very selective methylenation of **18** to form **20** is especially striking in view of our incidental finding that dibromocarbene adds exclusively to the 12,13-double bond of **18**, perhaps by way of a transition state with zwitterionic character ($Br_2C^{\delta-}$–C(12), C(13)–C(18)–C(17)$^{\delta+}$). The selective free-radical-induced cleavage of the cyclopropyl ring in **21** to form **22** represents a new approach to the introduction of oxygenated angular methyl groups. The completely specific hydrogenation of vinylcyclopropane **20** to δ-amyrin hexahydrobenzoate provides another route to angular methyl groups. Finally, the stereospecific reduction of **22** to form **23** demonstrates a new method for the hydroxyl-directed, stereocontrolled 1,4-reduction of 1,3-dienes which should prove to be of considerable utility.

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Supplementary Material Available: Characterization data for compounds shown in Schemes I and II (5 pages). Ordering information is given on any current masthead page.

(15) (a) Corey, E. J.; Ortiz de Montellano, P. R. *J. Am. Chem. Soc.* **1967**, *89*, 3362. (b) Ruzicka, L.; Eschenmoser, A.; Heusser, H. *Experientia* **1953**, *9*, 357.

(16) See also: Corey, E. J.; Sodeoka, M. *Tetrahedron Lett.* **1991**, *32*, 7005.

(17) Cf.: Bates, R. B.; Gosselink, D. W.; Kaczinski, J. A. *Tetrahedron Lett.* **1967**, 199.