Chiral Acetal-Initiated Asymmetric Pentacyclization. Enantioselective Synthesis of 18α(*H*)-Oleananes

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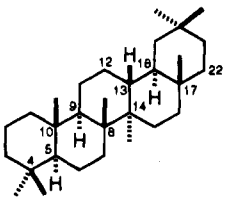
Received August 4, 1994®

Summary: Fluorine-assisted asymmetric pentacyclization of (*S*,*S*)-acetal **3** gave 18α(*H*)-oleanane **28b** as the major product in 59% isolated yield (86.5% de) and with retention of the fluorine atom at C13.

We recently reported the first total synthesis of a pentacyclic triterpenoid (racemic sophoradiol) employing the *pentacyclization* of an acyclic polyene substrate.[1] As an extension of this study an investigation was undertaken with the aim of realizing an enantioselective synthesis of representative oleananes in which the key step was a chiral acetal-initiated asymmetric pentacyclization.[2,3] Previous studies have all concentrated upon the construction of the olean-12-ene carbon framework,[1] and so a synthesis of the 18α(*H*)-oleananes,[4] e.g., **1**,[5] would provide additional insight into these pentacyclization processes and allow access to this ring system.



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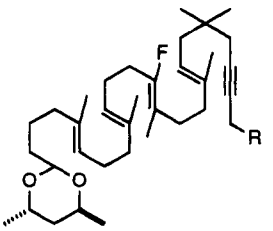
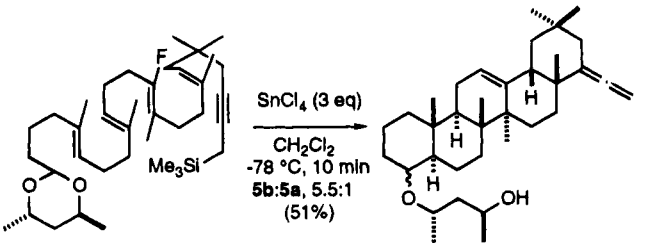


2: R = H
3: R = $SiMe_3$

Two complementary polyene acetals **2** and **3** were selected as substrates for cyclization studies. The polyenes share a common carbon framework which upon pentacyclization should yield the 18α(*H*)-oleanane ring system. Acetals **2** and **3** incorporate a fluorine atom cation-stabilizing auxiliary which has been shown to promote and control the cyclization.[1,2c,6] For example, treatment of racemic acetal **4** with tin(IV) chloride gave a separable mixture of C4 isomeric pentacycle alcohols **5** in 51% isolated yield (4β:4α, 5.5:1) (eq 1).[1c] It is



4 **5b**: $4\beta_{ax}$ **5a**: $4\alpha_{eq}$ (1)

important to note that no fluoropentacyclic products were isolated; these evidently underwent regioselective *in situ* dehydrofluorination to create the C12–13 olefinic bond.[7] Hence, cyclization of the corresponding acetal with the *pro*-C17–18 *trans*-olefin, i.e., **2** and **3**, was expected to yield the 18α(*H*)-pentacycle with the D/E anti-trans ring junction.

The synthesis of the cyclization substrates **2** and **3** was linear in design and was accomplished by the same basic strategy that was developed for the preparation of **4**.[1c] Alcohol **10** served as a branching point in the synthesis, leading either to substrate **2** or, after conversion to the trimethylsilyl derivative **18**, to substrate **3**. Thus, coupling of the sodium enolate of β-keto ester **6**[8] with the known allylic acetate **7**[6b] under palladium(0) catalysis gave **8** as predominantly the *trans*-isomer (83:17) in 85% yield (Scheme 1).[9] Decarboethoxylation of **8** to ketone **9** followed by reduction with $LiAlH_4$ provided alcohol **10** which was readily separable from the corresponding *pro*-C13–14 *cis*-isomer simply by column chromatography. Cyclopropylcarbinol **10** was rearranged under Brady–Julia conditions[8] to bromide **11** with high trans selectivity (97:3) and subsequent treatment of **11** with NaCN gave nitrile **12**, which was then reduced with DIBALH to aldehyde **13**. Reaction of **13** with CH_2=C(Me)MgBr gave allylic alcohol **14**, which underwent orthoester Claisen

† The X-ray crystallographic analyses reported herein were performed by F.S.T. and R.K.K. at the Department of Chemistry, Rensselaer Polytechnic Institute, Troy, NY 12180.

® Abstract published in *Advance ACS Abstracts,* October 1, 1994.

(1) (a) Fish, P. V.; Sudhakar, A. R.; Johnson, W. S. *Tetrahedron Lett.* **1993**, *34*, 7849–7852. (b) Fish, P. V.; Johnson, W. S. *Tetrahedron Lett.* **1994**, *35*, 1469–1472. (c) Fish, P. V.; Johnson, W. S. *J. Org. Chem.* **1994**, *59*, 2324–2335.

(2) (a) Johnson, W. S.; Elliot, J. D.; Hanson, G. *J. Am. Chem. Soc.* **1984**, *106*, 1138–1139. (b) Guay, D.; Johnson, W. S.; Schubert, U. *J. Org. Chem.* **1989**, *54*, 4731–4732. (c) Johnson, W. S.; Fletcher, V. R.; Chenera, B.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 497–504.

(3) For an enantioselective total synthesis of β-amyrin by the asymmetric tricyclization of a chiral epoxide substrate, see: Corey, E. J.; Lee, J. *J. Am. Chem. Soc.* **1993**, *115*, 8873–8874.

(4) (a) Dev, S.; Gupta, A. S.; Patwardhan, S. A. Triterpenoids. In *CRC Handbook of Terpenoids*; Dev, S., Ed.; CRC Press, Inc.: Boca Raton, FL, 1989; Vol. II, pp 7–61, 326–489. (b) Connolly, J. D.; Hill, R. A.; Ngadjui, B. T. *Nat. Prod. Rep.* **1994**, *11*, 91–117.

(5) 18α(*H*)-Oleanane (**1**), isolation from Nigerian crude oil: (a) Fowell, D. T.; Melsom, B. G.; Smith, G. W. *Acta Crystallogr.* **1978**, *B34*, 2244–2250. Synthesis from lupeol: (b) Corbett, R. E.; Ding, H. L. *J. Chem. Soc. C* **1971**, 1884–1885. The 18α(*H*)-oleananes are not really natural products in the usual sense; oleanane **1** is present in petroleum samples where it no doubt arose from natural 18β(*H*)-oleanenes in plant sediments by geologically induced isomerization and reduction. There are currently no known naturally occurring 18α(*H*)-oleananes as plant products. We are grateful to one of the reviewers for prompting clarification of this point.

(6) (a) Johnson, W. S.; Chenera, B.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 493–497. (b) Johnson, W. S.; Buchanan, R. A.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 504–515. (c) Johnson, W. S.; Plummer, M. S.; Reddy, S. P.; Bartlett, W. R. *J. Am. Chem. Soc.* **1993**, *115*, 515–521.

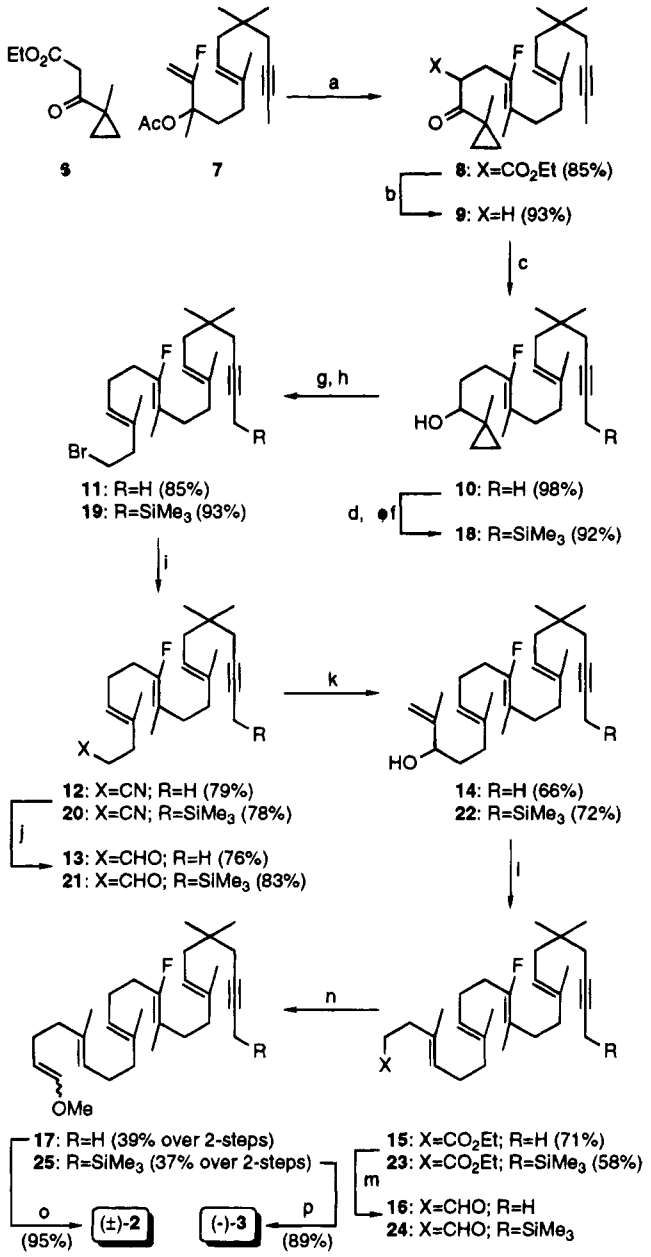
(7) Synthetic olean-12-ene **5** was unsuitably functionalized to allow conversion to any natural oleanane as it has not, as yet, proved possible to degrade the C22 allenyl group in the presence of the C12–13 alkene. It would be synthetically advantageous for the fluorine atom to be retained in the cyclization products in order to afford greater control over any subsequent synthetic manipulations.

(8) Brady, S. F.; Milton, M. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1968**, *90*, 2882–2889.

(9) Fish, P. V.; Reddy, P. S.; Lee, C. H.; Johnson, W. S. *Tetrahedron Lett.* **1992**, *33*, 8001–8004.

0022-3263/94/1959-6150$04.50/0

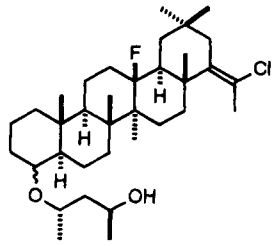
Scheme 1[a]



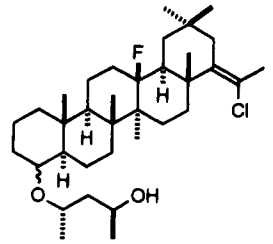
[a] Key: (a) **6**, NaH; $Pd(PPh_3)_4$, PPh_3; (b) NaOH; (c) $LiAlH_4$; (d) *t*-BuLi, TMEDA; (e) Me_3SiCl; (f) K_2CO_3; (g) PBr_3, LiBr, 2,6-lutidine; (h) $ZnBr_2$; (i) NaCN; (j) DIBALH then H_3O^+; (k) $CH_2{=}C(Me)MgBr$; (l) $MeC(OEt)_3$, H^+; (m) DIBALH; (n) $Ph_3P^+CH_2OMe\ Cl^-$, *s*-BuLi; (o) (±)-2,4-pentanediol, H^+; (p) (+)-(2*S*,4*S*)-pentanediol, H^+.

rearrangement[10] to ester **15** (*E*:*Z*, 95:5). Reduction of **15** with DIBALH and treatment of the resulting aldehyde **16** with (methoxymethyl)triphenylphosphorane gave the homologated enol ethers **17** (*E*:*Z*, 49:51), which underwent smooth acid-catalyzed acetalization with (±)-2,4-pentanediol to yield the (*E*,*E*,*Z*,*E*)-tetraene acetal (±)-**2**. The trimethylsilyl group of substrate **3** was most efficiently introduced by treatment of **10** with excess *t*-BuLi, trapping of the dianion with TMSCl, and then desilylation of the TMS ether with K_2CO_3/MeOH to furnish the propargylsilane **18**.[11] The elaboration of **18** to enol ethers **25** (*E*:*Z*, 50:50) followed the same synthetic sequence (Scheme 1) with similar yields and stereoselectivities, and then acid-catalyzed acetalization of **25** with (+)-(2*S*,4*S*)-pentanediol gave (*E*,*E*,*Z*,*E*)-tetraene (*S*,*S*)-acetal (−)-**3**.

Prior studies suggested that cyclization of acetals **2** and **3** would be most effectively achieved with tin(IV) chloride.[1c,2c] Thus, treatment of acetal **2** with $SnCl_4$ (3.0 equiv, CH_2Cl_2, −78 °C, 60 min), followed by quenching with NEt_3–MeOH and aqueous $NaHCO_3$, gave after flash chromatography pentacycle **26b** in 56% yield with *retention* of the fluorine atom at C13. Analysis of the crude reaction product mixture, principally by ^1H NMR, indicated that the minor cyclization products (<5%) included the 22(*Z*)-chloroethylidene isomer **27** and a trace amount of the corresponding C22 allene **28**, but predominantly consisted of products of partial cyclization. The 4α-alcohol **26a** was not observed as a product of the cyclization. The structure and relative configuration of **26b** were confirmed by X-ray structure determination of the purified crystals, mp 172–174 °C.



26b: 4β
26a: 4α



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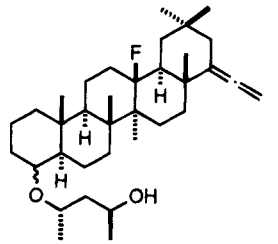
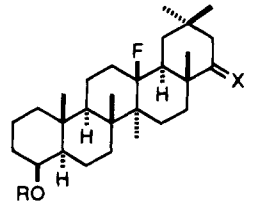


28b: 4β
28a: 4α



29b: R = H; X = C=CH2
30b: R = (*R*)-MTPA; X = C=CH2
31b: R = (*R*)-MTPA; X = O

Cyclization of acetal (−)-**3** with $SnCl_4$ under identical conditions (reaction time = 10 min) gave a crude product which contained **28b** and **28a** in the ratio 5:1 by ^1H NMR analysis. Column chromatography separated fluoropentacycle **28b** in 59% yield.[12] Further purification by recrystallization gave pure **28b**, mp 173–175 °C, $[\alpha]^{27}_D$ = +88° (*c* = 0.22, $CHCl_3$). The retention of the F-atom at C13 during Lewis acid promoted cyclization of **3** (and **2**) can be attributed to the lack of steric congestion of the carbon skeleton in the all-trans fluoropentacyclic product **28b** (and **26b**), and so there was no strong driving force for the elimination of HF (cf. **4** → **5**).[13]

In a separate sequence of reactions, the crude reaction product mixture from the cyclization of (−)-**3** (i.e., predominantly **28b**) was converted to the Mosher esters[14]

(10) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-t.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.
(11) Rajagopalan, S.; Zweifel, G. *Synthesis* **1984**, 111–112.
(12) Fluoropentacycle **28b** is suitably functionalized at C4, C13, and C22 to potentially allow conversion to **1**.
(13) For a detailed discussion of the factors that influence dehydrofluorination from related pentacycles, see refs 1c and 6.
(14) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.

31b by the following transformations:[15] (1) removal of the chiral auxiliary[2] by oxidation with PCC to the corresponding ketone, followed by KOH-catalyzed β-elimination to **29b**;[16] (2) esterification of the C4 hydroxyl with (+)-(*S*)-MTPA-Cl (pyridine, DMAP) to **30b**; and finally (3) ozonolysis of the C22 vinylidene to give **31b**. The optical purity of **31b** was determined by ^{1}H NMR analysis to be 86.5% ee. Except for the possibility of some enantioenrichment, it may be concluded that the cyclization **3** → **28b** proceeded with an asymmetric induction of 86.5%, which is consistent with previous results.[2] The relative configuration of **28b** follows from the unequivocally established constitution of the closely related pentacycle **26b** (X-ray analysis) and that the absolute configuration is that of the natural oleananes is almost certainly assured by the established stereochemical course of the cyclization of related chiral acetal polyenes.[2]

(15) This sequence of reactions was performed with a minimum of purification and characterization of the intermediates. Where chromatography was unavoidable, great care was taken (by GC analysis of all fractions) to ensure that no diastereomeric oleananes were separated.

(16) Removal of the auxiliary at C4 was also accompanied by base-promoted dehydrofluorination (ca. 20%) to yield predominantly the C12–13 olefin isomer.

Acknowledgment. We thank the National Institutes of Health (DK 03787) and the National Science Foundation for their support of this work. HRMS were recorded by the Regional Mass Spectrometric Service at the University of California, San Francisco.

Supplementary Material Available: Characterization data for compounds **8**–**31** and ORTEP plot for **26b** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.