A Short Enantioselective Total Synthesis of Dammarenediol II

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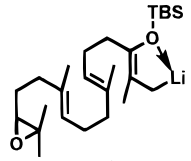
We report herein an enantioselective and unusually short synthesis of dammarenediol II (**1**), the primary product of the tetracyclization of (*S*)-2,3-oxidosqualene in plants,[1,2] and the plant analog of the mammalian sterol precursor protosterol,[3] hitherto a classical unsolved synthetic problem. Dammarenediol II is of considerable biosynthetic interest because of recent progress in the cloning of various (*S*)-2,3-oxidosqualene cyclase genes and related bioorganic studies.[4] In addition, dammarenediol has been found to have antiviral activity against herpes simplex.[5] The sequence which we have developed for the first total synthesis[6] of **1** is summarized in Scheme 1.

The element of enantiocontrol in the synthesis was based on the recent development of a mechanistically designed bis-cinchona alkaloid catalyst for the *terminal* dihydroxylation of *E*,*E*-farnesyl acetate with >120:1 position selectivity and 98:2 enantioselectivity to form diol **2** in 80% yield.[7] This key chiral intermediate was converted in 95% yield to (10*S*)-10,11-oxidofarnesol (**3**)[7] by selective mesylation of the 10-hydroxyl (1.5 equiv of methanesulfonyl chloride and 10 equiv of pyridine in CH_2Cl_2 at 23 °C for 12 h) and treatment with potassium carbonate in methanol at 23 °C for 6 h. Epoxy bromide **4** was prepared from **3** in a one-flask process consisting of primary mesylate formation (CH_3SO_2Cl, Et_3N, THF, −45 °C for 30 min) and further reaction with LiBr in THF solution at 0 °C for 2 h.

The next phase of the synthetic plan required the stereoselective elaboration of the chiral epoxy bromide **4** to *Z*-tetrasubstituted silyl enol ether **8**. Although there was no strong precedent for this task, the problem was solved in the following way. Acetyl-*tert*-butyldimethylsilane[8] and 2-amino-1-methoxypropane (Aldrich) were heated at reflux in benzene with continuous removal of water to give the corresponding imine **5**, bp 60−65 °C at 1.5 Torr (85%). Deprotonation of **5** with 1.05 equiv of lithium diisopropylamide (LDA) in THF at −30 °C initially and then at 0 °C for 30 min afforded the corresponding lithium azaenolate (as a yellow solution) which was cooled to −30 °C and treated with epoxy bromide **4** (at −30 °C initially and then at −30° to −10 °C over 1 h) to produce the acylsilane **6** after imine hydrolysis (biphasic mixture of pentane and aqueous HOAc−NaOAc buffer, stirring, 23 °C, 2 h) and isolation. This reaction represents a very practical route to acylsilanes.[9] Although imino silanes have previously been obtained by sequential reaction of isocyanides with alkyllithium reagents and trimethylchlorosilane, their selective hydrolysis to acylsilanes had not been accomplished.[10,11] Acylsilane **6** was treated with 2-lithiopropene in ether at −78 °C for 30 min and then with iodo thioketal **7**[12] in THF−ether at −78 °C for 2 h to give stereospecifically the *Z*-tetrasubstituted enol silyl ether **8** in 60% isolated yield after purification by column chromatography. ^{1}H NMR and ^{13}C NMR analysis of both crude and chromatographed product demonstrated the absence of the isomeric *E*-tetrasubstituted enol ether. The use of the trimethylsilyl analog of **6** in this process afforded a 1:1 mixture of *E*- and *Z*-tetrasubstituted enol ethers, paralleling the results noted by Reich for a tetrasubstituted case.[13] The stereoselectivity of formation of **8** may be due to a chelated structure (**A**) for the intermediate lithio species analogous to chelated magnesium structures proposed by Kuwajima.[14]



A

The next phase of the total synthesis of **1** was the construction of the tetracyclic ketone **10**. Although the formation of this intermediate is possible, in principle, through the use of a cation-olefin tetracyclization of an acyclic epoxy triene precursor (biomimetic type route), in practice efficient tetracyclizations of the required type have not been realized to date.[15] Consequently, we utilized a strategy involving a favorably arranged cation-olefin tricyclization which leads to an intermediate that allows aldol cyclization to form the fourth ring.[16] Lewis acid induced cyclization of the epoxy triene **8** in CH_2Cl_2 at −95 °C with 1.5 equiv of a 1 M solution of methylaluminum dichloride in hexane for 10 min followed by desilylation with a catalytic amount of 48% aqueous HF in CH_3CN at 23 °C for 45 min and thioketal cleavage with iodobenzene-*bis*(trifluoroacetate) in 9:1:1 MeOH−H_2O−*i*-PrOH at 0 °C for 45 min produced, after chromatographic purification on silica gel, the tetracyclic hydroxy diketone **9**, mp 164−165 °C, $[\alpha]^{23}_D$ +8.0 (c = 0.2 in CH_2Cl_2) in 42% overall yield (probably not optimal). This alcohol was converted to the corresponding phenylcarbamate (92% yield by reaction with phenyl isocyanate in pyridine) which was cyclized by heating at reflux in C_6H_6 with a catalytic amount of *p*-toluenesulfonic acid to provide the tetracyclic α,*β*-enone **10** in 84% yield.[17]

(1) (a) Mills, J. S. *Chem. Ind. (London)* **1956**, 189. (b) Mills, J. S. *J. Chem. Soc.* **1956**, 2196. (c) Lehn, J.-M.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1962**, 1137. (d) Biftu, T.; Stevenson, R. *J. Chem. Soc., Perkin Trans. 1* **1978**, 360. (e) Biellmann, J.-F. *Bull. Soc. Chim. Fr.* **1967**, 3459.

(2) Dammarenediol I, the (20*R*)-diastereomer of dammarenediol, also occurs naturally.[1]

(3) (a) Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1990**, *112*, 6429. (b) Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1991**, *113*, 4025. (c) Corey, E. J.; Virgil, S. C.; Sarshar, S. *J. Am. Chem. Soc.* **1991**, *113*, 8171.

(4) Baker, C. H.; Matsuda, S. P. T.; Liu, D. R.; Corey, E. J. *Biochem. Biophys. Res. Commun.* **1995**, *213*, 154 and references cited therein.

(5) Poehland, B. L.; Carte, B. K.; Francis, T. A.; Hyland, L. J.; Allaudeen, H. S.; Troupe, N. *J. Nat. Prod.* **1987**, *50*, 706.

(6) A partial synthesis of the dammarenediol II from the naturally occurring pentacyclic triterpene hydroxyhopanone has been reported. See: Fujimoto, H.; Tanaka, O. *Chem. Pharm. Bull.* **1974**, *22*, 1213; **1970**, *18*, 1440.

(7) Corey, E. J.; Noe, M. C.; Lin, S. *Tetrahedron Lett.* **1995**, *36*, 8741.

(8) For the method of preparation, see: Nowick, J. S.; Danheiser, R. L. *Tetrahedron* **1988**, *44*, 4113.

(9) For reviews on the synthesis of acylsilanes, see: (a) Ricci, A.; Degl'Innocenti, A. *Synthesis* **1989**, 647. (b) Page, P. C. B.; Klair, S. S.; Rosenthal, S. *Chem. Soc. Rev.* **1990**, *19*, 147.

(10) Niznik, G. E.; Morrison, W. H., III; Walborsky, H. M. *J. Org. Chem.* **1974**, *39*, 600.

(11) It should also be mentioned that the alkylation of the metal enolates of acylsilanes with alkyl halides is generally complicated by the formation of both mono- and dialkylation products.

(12) Iodo thioketal **7** was prepared from 2-hydroxyethyl-2-methyldithiolane (Rama Rao, A. V.; Venkatswamy, G.; Javeed, S. M.; Deshpande, V. H.; Rao, B. R. *J. Org. Chem.* **1983**, *48*, 1552) by reaction with triphenylphosphine, iodine, and imidazole in CH_2Cl_2 at 23 °C for 17 h.

(13) Reich, H. J.; Olson, R. E.; Clark, M. C. *J. Am. Chem. Soc.* **1980**, *102*, 1423.

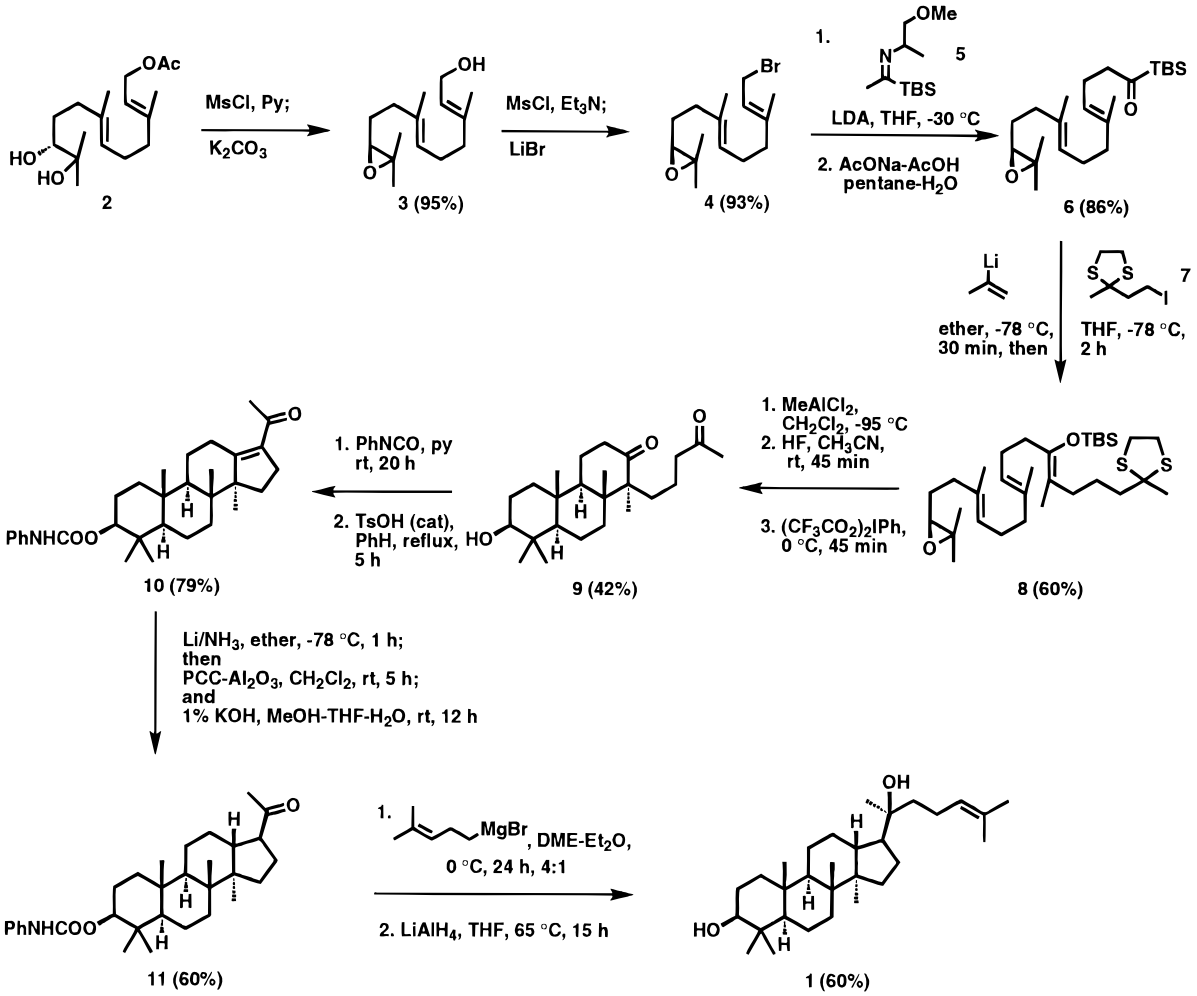
(14) Enda, J.; Kuwajima, I. *J. Am. Chem. Soc.* **1985**, *107*, 5495.

(15) For background, see: (a) Taylor, S. K. *Org. Prep. Proced. Intl.* **1992**, *24*, 245. (b) Johnson, W. S. *Tetrahedron* **1991**, *47* (41), xi. (c) Corey, E. J.; Lee. J.; Liu, D. R. *Tetrahedron Lett.* **1994**, *35*, 9149. (d) Corey, E. J.; Lee. J. *J. Am. Chem. Soc.* **1993**, *115*, 8873. (e) Johnson, W. S.; Plummer, M. S.; Reddy, S. P.; Bartlett, W. R. *J. Am. Chem. Soc.* **1993**, *115*, 515. (f) Tanis, S. P.; Chuang, Y.-H.; Head, D. B. *J. Org. Chem.* **1988**, *53*, 4929.

(16) To the best of our knowledge, this approach has not previously been demonstrated despite the vast amount of effort which has been directed at the synthesis of steroid-like ring systems.

S0002-7863(96)02080-X CCC: $12.00

Scheme 1. Enantioselective Synthesis of Dammarenediol II



The transformation of enone **10** into dammarenediol II was accomplished using standard procedures. Reduction of enone **10** with lithium in liquid ammonia at −78 °C for 1 h gave a crude reduction product which was stirred briefly with pyridinium chlorochromate on alumina (to oxidize a small amount of secondary alcohol), treated with 1% KOH in 1:1:1 CH_3OH-H_2O-THF (to effect equilibration of diastereomers at C(17) to the more stable 17β-acetyl arrangement) and chromatographed on silica gel which provided the saturated tetracyclic ketone **11** in 60% yield. Reaction of **11** with 4-methyl-3-hexenylmagnesium bromide in dimethoxyethane−ether at 0 °C for 24 h produced a mixture of C(20)-diastereomeric alcohols (ratio 20*S*:20*R*, 4:1) which was deprotected by heating at reflux with a THF solution of $LiAlH_4$ and separated chromatographically on silica gel (50:1 C_6H_6−acetone for elution) to give dammarenediol II (**1**) in 60% overall yield.[18] Totally synthetic **1** was recrystallized from EtOH−H_2O to give long colorless needles, mp 75−76 °C (mixture mp with an authentic sample 75−76 °C), identical with naturally derived dammarenediol II by ^1H NMR (at 500 MHz) and ^{13}C NMR (at 125 MHz) spectra, IR spectrum, and TLC chromatographic behavior on silica gel; $[\alpha]^{23}_D$ +40 (c = 0.04 in $CHCl_3$).

There are a number of noteworthy features of the synthesis of dammarenediol II which is described herein, apart from its brevity and stereochemical control. It demonstrates the use of the now readily available chiral epoxide **2**[7] to fix the absolute and relative stereochemistry of the final product **1**. It illustrates the power and stereoselectivity of the three-component coupling which converts acylsilane **6** to silyl enol ether **8** and also a very useful synthesis of **6**. The combined use of cation-olefin polyannulation with the aldol cyclization clearly represents an effective synthetic tactic for tetraannulation.

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Supporting Information Available: Experimental procedures and characterization data (9 pages). See any current masthead page for ordering and Internet access instructions.

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(17) The phenylcarbamate moiety survived the vigorous acid treatment required for the acid-catalyzed aldol conversion to **10** in contrast to other derivatives such as silyl ethers or carboxylic esters.

(18) Dammarenediol I was obtained from the later chromatographic fractions.