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First Demonstration of a Carbocation-Olefin Cyclization Route to the Lanosterol Series

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Summary: *A silicon-assisted double carbocation-olefin cyclization reaction was used as the key step (**10** → **11**) in a simple, convergent and enantioselective total synthesis of lanostenol (**1**).*

The only documented synthetic route to compounds in the lanosterol series is an extraordinary concatenation of two long sequences: (1) the famous Woodward total synthesis of cholesterol (actually as a mixture of the natural 20*R* form and the 20*S* diastereomer)[1] and (2) a multistep conversion of cholesterol to lanostenol (desmosterol, 24,25-dihydrolanosterol, **1**).[2] A series of further reactions provided a synthetic connection between lanostenol and lanosterol.[2] In contrast, lanosterol is biosynthesized in a single, exquisitely economical and effective step from (*S*)-2,3-oxidosqualene,[3] a process which is catalyzed by a single 83-kDa enzyme.[4] For more than four decades synthetic chemists have been confronted by the twin challenges of understanding the nature of the enzymatic process catalyzed by lanosterol synthase and duplicating in a chemical system the remarkable conversion of 2,3-oxidosqualene to lanosterol via carbocationic cyclization with rearrangement. Both goals are still elusive, although considerable progress has been made in the harnessing and application of carbocation-olefin cyclizations to the synthesis of polycyclic terpenoids and steroids.[5] Described herein is another step along this long road, a short and effective chemical synthesis of a member of the lanosterol series, lanostenol (desmosterol, 24,25-dihydrolanosterol, **1**) by a carbocation-olefin cyclization route. This research has produced new insights with regard to carbocation-olefin cyclizations which should stimulate further advances.

The convergent route to the lanosterol family is illustrated for the case of **1** in the accompanying scheme, the starting points for which are the readily available Grundemann ketone (**3**)[6] and (*S*)-6,7-oxidogeraniol (**6**).[7] Conversion of **3** to the trimethylsilyl (TMS) enol ether,[8] Simmons-Smith methylenation[9] and base-catalyzed cleavage of the resulting cyclopropanol derivative[9] provided the *trans*-fused α-methylated ketone **4**,[10] which was transformed into the vinyl iodide **5** by Barton's procedure.[11] (*S*)-6,7-Oxidogeraniol[7] was homologated to (*S*)-7,8-oxidohomogeraniol by Leopold's method[12] and, after oxidation of the latter, the chiral aldehyde **8** was obtained efficiently.

Conversion of the vinyl iodide **5** to the corresponding vinyllithium reagent and addition to a solution of the aldehyde **8** and $MgBr_2$ in ether resulted in smooth coupling to form in 76% yield a readily separable (by silica gel

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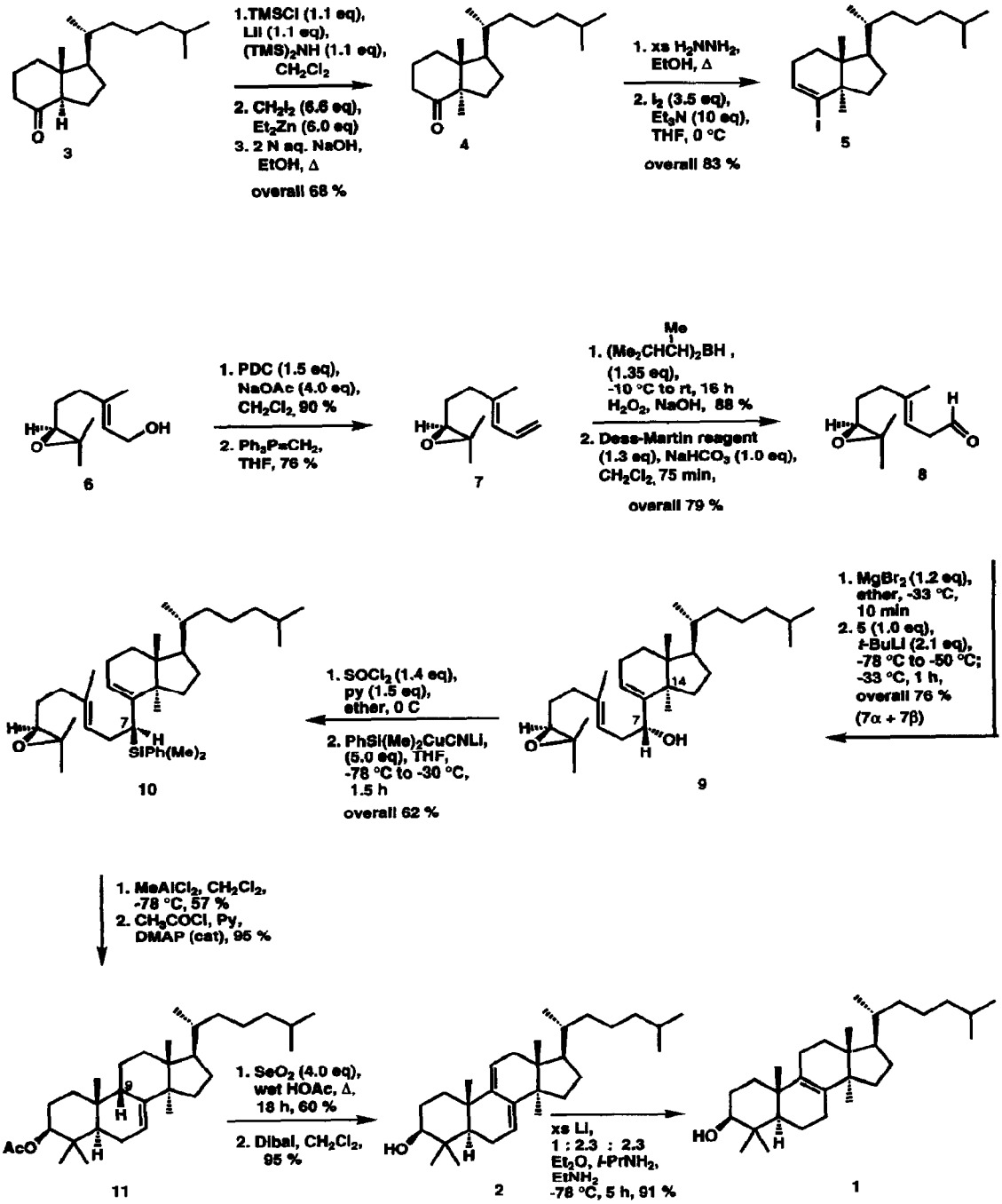
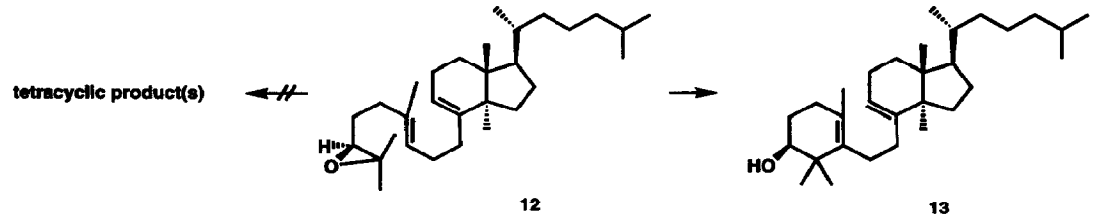

1.TMSCl (1.1 eq), LiI (1.1 eq), (TMS)2NH (1.1 eq), CH2Cl2
2. CH2I2 (6.6 eq), Et2Zn (6.0 eq)
3. 2 N aq. NaOH, EtOH, Δ
overall 68 %
1. xs H2NNH2, EtOH, Δ
2. I2 (3.5 eq), Et3N (10 eq), THF, 0 °C
overall 83 %
1. PDC (1.5 eq), NaOAc (4.0 eq), CH2Cl2, 90 %
2. Ph3P=CH2, THF, 76 %
1. (Me2CHCH)2BH, (1.35 eq), -10 °C to rt, 16 h H2O2, NaOH, 88 %
2. Dess-Martin reagent (1.3 eq), NaHCO3 (1.0 eq), CH2Cl2, 75 min,
overall 79 %
1. MgBr2 (1.2 eq), ether, -33 °C, 10 min
2. 5 (1.0 eq), t-BuLi (2.1 eq), -78 °C to -50 °C; -33 °C, 1 h,
overall 76 %
(7α + 7β)
1. SOCl2 (1.4 eq), py (1.5 eq), ether, 0 C
2. PhSi(Me)2CuCNLi, (5.0 eq), THF, -78 °C to -30 °C, 1.5 h
overall 62 %
1. MeAlCl2, CH2Cl2, -78 °C, 57 %
2. CH3COCl, Py, DMAP (cat), 95 %
1. SeO2 (4.0 eq), wet HOAc, Δ, 18 h, 60 %
2. Dibal, CH2Cl2, 95 %
xs Li, 1 : 2.3 : 2.3 Et2O, i-PrNH2, EtNH2 -78 °C, 5 h, 91 %
3
4
5
6
7
8
9
10
11
2
1

chromatography) 1 : 1 mixture of **9** and the 7β-diastereomer.[13] The 7β-diastereomer of **9** was converted to **9** by sequential oxidation with the Dess-Martin periodinane and reduction of the resulting ketone with 5 equiv of $NaBH_4$ and 1.1 equiv of $CeCl_3$ in MeOH at -60 °C (6 : 1 ratio, 7α : 7β). The allylic 7α-alcohol **9** was transformed via an intermediate allylic chloride (unstable) to the allylic 7β-silane **10** using the reagent $PhSi(Me_2)CuCNLi$.[14,15] Reaction of **10** at -78 °C with $MeAlCl_2$ in CH_2Cl_2, acetylation and purification by silica gel chromatography afforded as major product the tetracyclic acetate **11** (55% over two steps). The 9β-H stereochemistry has been assigned to **11** on the basis of (1) the two step conversion to dihydroagnosterol (**2**) and (2) non-identity with a sample of the 9α-diastereomer of **11** which was obtained both from the reduction of **2** with Li–NH_3–THF[16] and the partial isomerization of dihydrolanosterol with HCl–$CHCl_3$.[17] The final step in the synthesis of lanostenol (**1**) was the reduction of **2** with Li in Et_2O, *i*-$PrNH_2$, $EtNH_2$ at -78 °C which afforded after chromatography **1** (91%) along with a small amount of the 9α-diastereomer of **11**.[18] Recrystallization produced pure **1**, mp 148-150 °C, $[\alpha]_D^{23}$ +56.3° (c=0.5, $CHCl_3$), identical in all respects (including 500 MHz ^1H NMR and ^{13}C NMR, FTIR, and MS) with an authentic sample prepared by hydrogenation of pure lanosterol over Pd–C.

The 7α-silyl diastereomer of **10** was synthesized from the 7β-OH diastereomer of **9** in two steps paralleling the conversion of **9** to **10**. Reaction of the 7α-silyl diastereomer of **10** with $MeAlCl_2$ in CH_2Cl_2 at -78 °C gave only a low yield (*ca.* 7%) of tetracyclic product, which after acetylation and chromatography on silica gel was identified as the 9α-H diastereomer of **11**. Cyclization experiments under a variety of conditions were also conducted on **12**, the analog of **10** lacking the 7-silyl substituent, but no trace of tetracyclic product could be detected after careful chromatographic and spectroscopic analysis, using various Lewis acids (BCl_3, $MeAlCl_2$, Me_2AlCl, BF_3) in CH_2Cl_2 at either -78 °C or -94 °C. One minor product which was chromatographically similar to **1** was isolated and identified as the tricyclic diene **13**. We suspect that this product might have been encountered earlier by van Tamelen et. al. and misidentified as dihydrolanosterol.[19] The failure of the cyclization process with **12** to yield tetracyclic product underscores the crucial role of silyl assistance in the transformation of **10** to **11**.



12 **13**

The formation of **11** from **10** is clearly the result of a boat-like transition state for the formation of the B-ring. Although chair-like transition states are normally highly favored in the formation of fused six-membered rings by carbocation-olefin cyclization, assistance by the allylic silane clearly can alter this preference. We interpret the less efficient cyclization reaction of the 7α-diastereomer of **10**, which can proceed via a chair B-ring transition state with *anti*- S_E2' stereochemistry, to be a consequence of an unfavorable steric repulsion between the 7α-silyl group and the 14α-methyl substituent. Thus, the use of silicon-assistance in carbocation-olefin polycyclizations may well be limited in scope to substrates which are free of such adverse steric interactions.[20]

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10. Approximately 5% of the *cis*-fused diastereomer of **4** was also produced. The stereochemical assignments for **4**, $[\alpha]_D^{23}$ -38° (c=1.2, $CHCl_3$), and the *cis*-fused isomer, $[\alpha]_D^{23}$ +64° (c=1, $CHCl_3$), are supported by these observed optical rotations and application of the octant rule.
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15. The 7α-stereochemistry of the allylic silane **10** has not been proved, and the assignment of configuration rests on the conversion to **11** (9β-H) and the assumption of an *anti* S_E2' pathway for the reaction **10** → **11**. See Buckle, M. J. C.; Fleming, E.; Gil, S. *Tetrahedron Letters* **1992**, *33*, 4479 and refs. cited therein.
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