MACRORING CONTRACTION METHODOLOGY. 2. TOTAL SYNTHESIS OF HAAGENOLIDE BY [2,3]-WITTIG REARRANGEMENT OF 13-MEMBERED DIALLYLIC ETHER[1]

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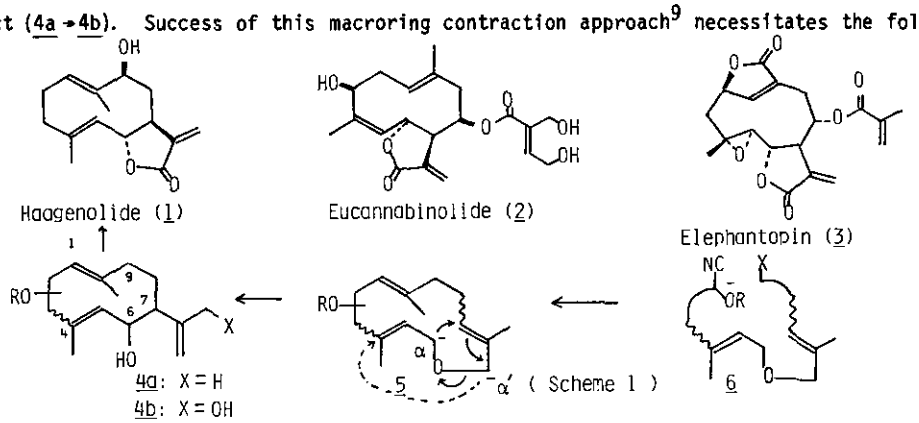
Dedicated to Professor G. Stork on the occasion of his 65th birthday.
Columbia University *(1971-1976), **(1957-1960)

Abstract —— A new route to construct the carbon skeleton of Haagenolide is described wherein the 13-membered diallylic ether 17, prepared by the cyanohydrin methodology, undergoes [2,3]-Wittig rearrangement to give the ten-membered carbocycles.

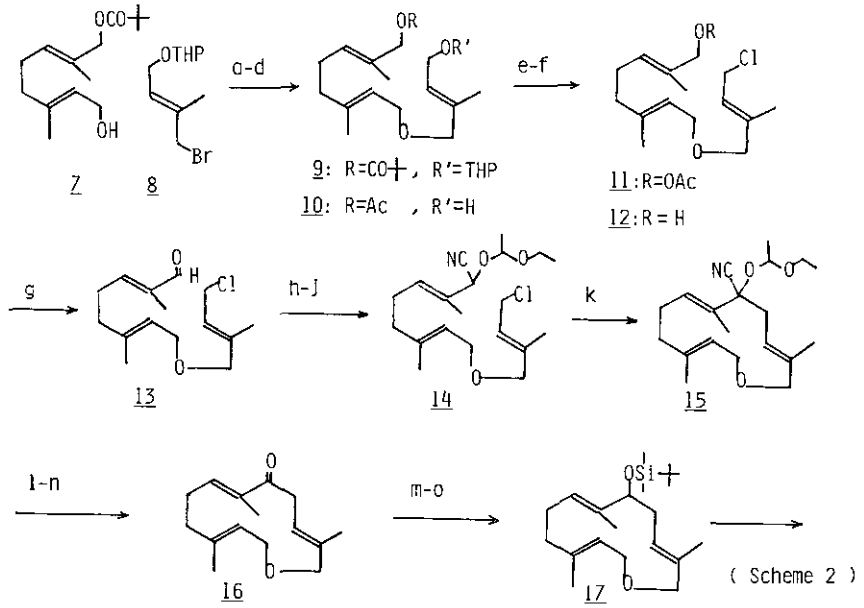
Previous attempts at macrocarbocyclic construction involve mostly indirect approaches such as ring expansion[2] (or cleavage[3]) and direct macrocyclization methodologies.[4] However, if macrocarbocycles are easily prepared, their contractions to medium-membered rings can be considered as the third methodology[5] which can simultaneously construct the carbon skeleton of macrocycles and induce the required stereochemistry. This type of stereocontrol might offer good methodology for syntheses of a large number of biologically active sesquiterpene lactones,[6] including haagenolide (1), eucannabinolide (2), and elephantopin (3). In this communication we wish to report the stereoselective synthesis of haagenolide as outlined in Scheme 1. Key steps in this synthesis are the [2,3]-Wittig rearrangement[7] of *13-membered diallylic ether to construct the ten-membered ring* (5 → 4a), the intramolecular alkylation of the protected cyanohydrin[8,4a] to give the macrocyclic ether (6 → 5), and the regioselective allylic oxidation of the isopropenyl group of the rearrangement product (4a → 4b). Success of this macroring contraction approach[9] necessitates the following



(Scheme 1)

three selectivities in the [2,3]-Wittig rearrangement; (1) the periselectivity, (2) the regioselectivity (α vs α' lithiation) in the ether 5, and (3) the remote control of stereoselectivity by the C(9)-silyloxy group [relative stereochemistry among C(6), C(7), and C(9)], as well as the E-geometry of C(4,5)-olefin in the rearrangement product 4a.

Thus the 13-membered diallylic ether 17 was our initial synthetic target and its preparative method is summarized in Scheme 2. The allylic alcohol 7 was easily prepared from geranyl acetate in three steps [SeO_2-t-BuOOH,[10] Me_3CCOCl/Py, K_2CO_3/MeOH]. O-alkylation of 7 with the bromide 8, reduction of the ester 9, acetylation of the resultant allylic alcohol, and removal of the tetrahydropyranyl group, gave the alcohol 10 in 57% overall yield. The allylic chlorination (98% yield) of 10, methanolysis of the acetate 11, and oxidation of the resultant allylic alcohol 12 gave the enal 13 in 69% overall yield from 11 ; ^{1}H-nmr ($CDCl_3$), 9.38 (brs, 1H), 1.76 (brs, 2xMe), 1.70 (brs, Me). The 1,2-addition of trimethylsilyl cyanide[11] to the enal 13, removal of the trimethylsilyl group from the adduct, and reprotection of the resultant cyanohydrin with ethyl vinyl ether gave the protected cyanohydrin 14 in 90% overall yield. Cyclization to the 13-membered ring 15 was effected in 80% yield by addition of 14 (0.65 mmol) in THF (10 ml) to a solution of $NaN(SiMe_3)_2$ (3.3 mmol) in THF (20 ml) over 2 h at 65°C. Acid-catalyzed removal of ethoxyethyl group of the cyclized product 15 and subsequent base treatment of the resultant cyanohydrin gave the enone 16 in 90% overall yield; ^{13}C-nmr ($CDCl_3$) 201.3, 146.0, 135.8, 135.6, 135.3, 126.1, 121.3, 78.7, 69.0, 40.3,

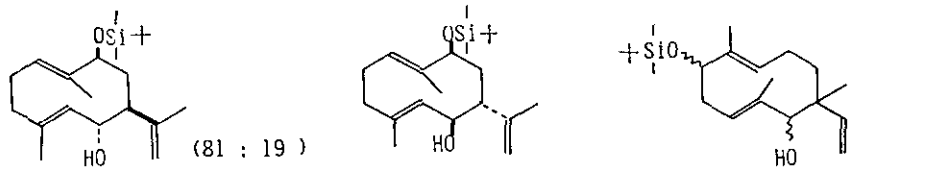


(Scheme 2)

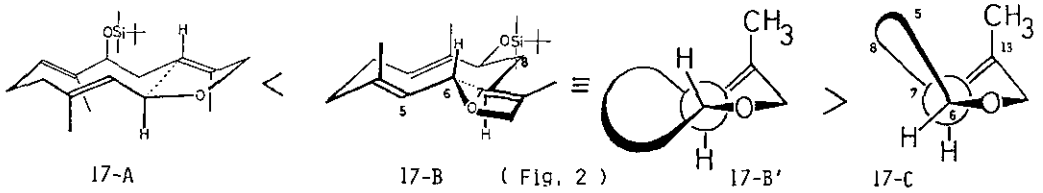
(a)KOH,Bu_4NI,H_2O,RT,1h; (b)$LiAlH_4$,Et_2O,0°C; (c)Ac_2O,Py,0°C; (d)PPTS,MeOH,40°C,3h; (e)PPh_3, CCl_4,76°C,12h; (f)K_2CO_3,MeOH,0°C,30 min; (g)MnO_2,hexane,RT,20h; (h)Me_3SiCN,KCN-18-crown-6, 0°C,1h; (i)$Me_3(PhCH_2)NF$,THF,RT,1h; (j)$CH_2CHOCH_2CH_3$,p-TsOH,CH_2Cl_2,0°C,1h; (k)$NaN(SiMe_3)_2$, THF,65°C,2h; (l)PPTS,MeOH,40°C,2h; (n)2%aq.NaOH,0°C,1 min; (m)$(i\text{-}Bu)_2AlH$,THF,-40°C,5min; (o)$(t\text{-}Bu)Me_2SiCl$,DMF,RT,1.5h

38.0, 25.8, 15.0, 14.2, 11.1. The reduction of ketone 16 and subsequent protection of the resultant allylic alcohol gave the t-butyldimethylsilyloxy ether 17 in 85% overall yield.

The [2,3]-Wittig rearrangement was carried out in the following way. The ether 17 was metalated in Et_2O with t-BuLi at -70°C under nitrogen and the resultant yellow solution was stirred for another 24 h at -70°C. Then the reaction mixture was allowed to warm over 30 min to room temp and quenched with aq NH_4Cl solution. After the usual work-up, a 4 : 1 mixture of [2,3]-rearrangement products 18 and 19,[12] derived via α-lithiation, was obtained in 43% yield, and the regioisomer 20[13] via α'-lithiation was also formed in 47% yield. None of [1,2]- and [1,4]-rearrangement products was detected in a crude reaction mixture by HPLC analysis. Thus the periselectivity and the remote stereoselectivity, except the regioselectivity, were excellent. Consideration of a probable transition state geometry for the observed remote stereocontrol by C(9)-silyloxy group suggested that the conformer 17-B having pseudo-equatorial silyloxy group would be more stable than the conformer 17-A containing pseudo-axial silyloxy group (Fig.2). Moreover, the high degree of trans-selection at C(6) and C(7) in this rearrangement can be tentatively explained as follows. The transition state developed from the geometry 17-C adopts the unfavorable conformation which has the 1,2-interaction arising from C(6-5) and C(7-8) C-C bonds, and likewise the 1,3-interaction between C(6-5) and C(13)-Me. While the transition state, formed from the geometry 17-B', has none of these steric interactions. Therefore the rearrangement proceeds in such a way to make two adjacent larger groups, C(6-5) and C(7-8) C-C bond, in the five-membered transition state trans to each other (Fig.2).



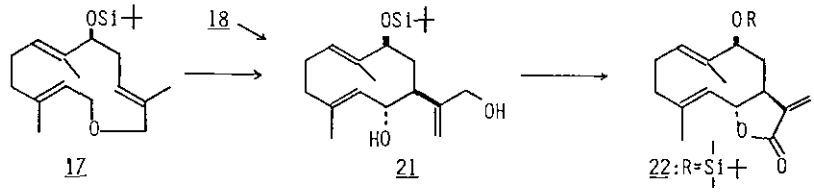
(Fig. 1)



(Fig. 2)

The above discussion was confirmed by conversion of 18 to haagenolide as follows (Scheme 3). Allylic lithiation of the isopropenyl moiety in 18 with sec-BuLi in the presence of TMEDA at -70°C in Et_2O, oxidation of the resultant lithiated species, followed by reductive work-up with Na_2SO_3 gave the desired allylic alcohol 21 in 60% yield[14]; ^1H-nmr ($CDCl_3$) 5.08 (d, J=12.6, 2H), 4.15

(brs, 2H), 1.65 (s, 3H), 1.42 (s, 3H) and no lithiation of olefinic methyls in the ring took place.[15] Based on such regioselectivity in the lithiation, we next attempted a one-pot process for the [2,3]-Wittig rearrangement and allylic oxidation. Treatment of 17 with sec-BuLi at -70°C in Et_2O, addition of TMEDA, introduction of oxygen to the reaction mixture, and final reductive work-up with Na_2SO_3 gave the desired diol 21 in 25% overall yield.[16] Oxidation of 21 with MnO_2 in Et_2O at room temp for 12 h gave directly the α-methylene δ-lactone 22 in 80% overall yield. Desilylation of 22 with Bu_4NF gave haagenolide (1). The nmr spectral data of the synthetic haagenolide; ^{1}H-nmr (Py-d_5) 6.34 (d, J=3.5, 1H), 5.53 (d, J=3.5, 1H), 4.70 (brd, C(5), C(6)), 4.41 (dd, J=3.1, 10.8, C(9)) and its acetate ; ^{1}H-nmr ($CDCl_3$) 6.30 (d, J=3.5, 1H), 5.56 (d, J=3.3, 1H), 5.22 (dd, J=3, 10, C(9)), 4.6 (d, J=10, C(5)), 4.56 (dd, J=8.5,10, C(6)), 2.06 (S, Me), 1.73 (S, Me), 1.48 (S, Me); mp 162-165°C (n-hexane-ether) were identical with those of natural haagenolide and its acetate.[17]



17 21

(Scheme 3)

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13. The stereochemistry was not determined.
14. The alcohol 18 was recovered in 35% yield.
15. Electrophilic reactions such as epoxidation and hydroboration using m-CPBA and 9-BBN proceeded at the most reactive C(1,10)-olefin. The selective lithiation at isopropenyl group necessitates the free hydroxy group at C(6).
16. The rearrangement products 18 and 20 were obtained in 10 and 47% yields respectively.
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