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Role Of Radical Initiated Cyclisation Reactions In The Synthesis Of Artemisinin Based Novel Ring Skeletons+.

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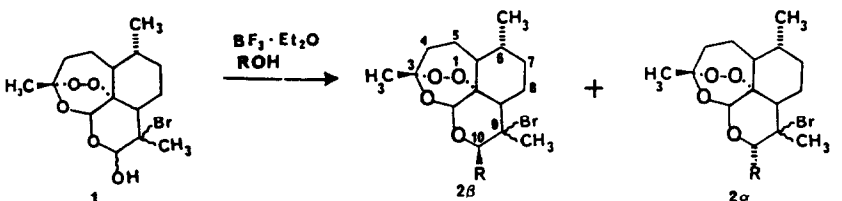
ABSTRACT:- Refluxing the propargyl ether **2c** with nBu_3SnH/AIBN in toluene gave the clean single stereoisomer **3**. Similarly the other isomer **2d** underwent a smooth radical cyclisation to give **5**. The allyl ether **2e** gave **6**, a 1,2-cis 1,5-trans product, under similar condition whereas the ether **2f** gave two products, namely, Compound **7** (1,2-cis 1,5-cis) and Compound **8** (1,2-cis 1,5-trans).

In connection with the synthesis of different artemisinin[1] based ring skeletons for antimalarial screening, we report herein the synthesis of a novel ring system using tin mediated radical cyclisation reactions. Use of the radical mediated ring closure reaction became more prominence because of its simplicity and high stereoselectivity which enabled to synthesis many natural products[2].

Treatment of the bromohydrin[3] **1** with primary alcohols in the presence of $BF_3.Et_2O$ gave the bromo ethers **2a-2f** (Scheme 1). In each

Scheme 1.



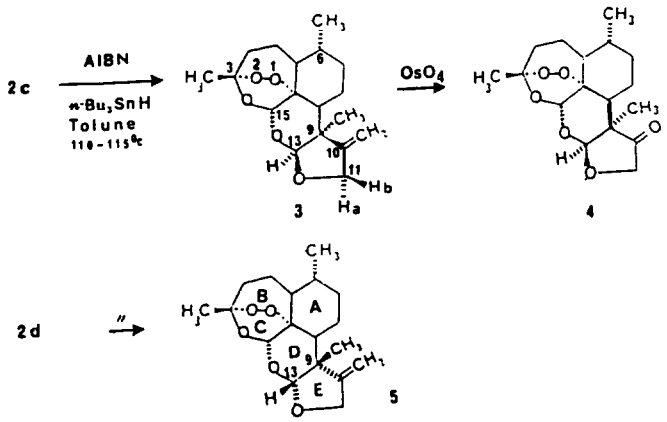
R	2	
OC_2H_5	a	b
$OCH_2C{\equiv}CH$	c	d
$OCH_2CH{=}CH_2$	e	f

+Dedicated to Prof. C. N. Pillai on the occasion of his 60th birthday.

case two diastereoisomers were formed in ratios of 4:1, separated by flash column chromotography, the major[4] 10 ß acetal having the higher R_F. The above assignment was further confirmed by the following experiment. The bromoether **2a**, the major isomer, was reduced using nBu_3SnH/AIBN to give arteether[5], a known derivative, thus confirming the relative stereochemistry at the 10- position to be ß. However the relative stereochemistry at the 9-position was not confirmed because it was not essential at this point.

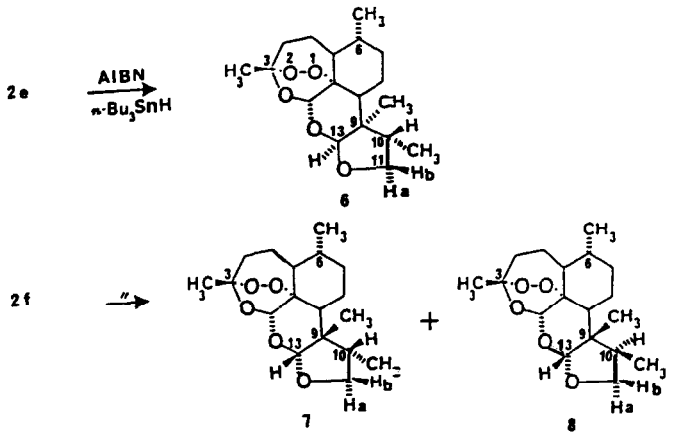
Refluxing the propargyl ether **2c** with nBu_3SnH/AIBN in toluene at 110°c for 18hrs gave the clean single stereoisomer **3** in 82 % yield as a solid after usual workup[6]. The exo methylene derivative **3** underwent oxidation in the presence of OsO_4 to give the keto compound **4** in 30% yield. Similarly the other isomer **2d** underwent a smooth radical cyclisation reaction under similar condition to give **5** as a solid[7].

Scheme 2



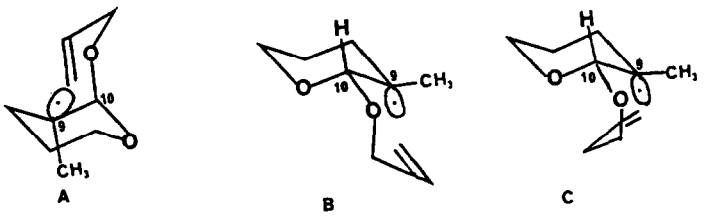
The allyl ether **2e** underwent cyclisation reaction to give exclusively **6** in 75% yield[8]. The 13-proton of the cyclic product **6** displayed NOE upon irradiation of 9-methyl group, thus confirming the relative configuration of 13-H and 9-methyl group to be α. Irradiation of the signal at δ 3.44(H_{11a}) showed NOE on 13-H and 10-methyl signals. Similar selective NOE experiments (irradiation of 10-methyl and of 11a-H) confirm the relative configuration at 13-H, 10-methyl, 9-methyl and 11a-H is α.[1,2-cis 1,5-trans product, structure **6**]. On the contrary the radical cyclisation of **2f** gave two products, one having a higher Rf tlc value and the other one with lower Rf value. On the basis of the spectral data[9], the structure **7** [1,2-cis 1,5-cis product] was assigned to the upper moving spot (yield 30%). Selective NOE experiments support

Scheme 3



its structure. The structure **8** was assigned to the product having lower Rf value[10](yield 21%) (Scheme 3).

The D-ring of the Compound **2e** exists in chair form and the 10β-OR group occupy the axial position and in the case of the Compound **2f**, the 10α-OR group occupy the equatorial position similar to the reported 10-ethers of dihydroartemisinin[11]. The radical **A** derived from bromoacetal **2e** should cyclise through a "chair like[12]" transition state to give **6** , while the radicals **B** and **C** derived from bromo acetal **2f** should cyclise through either "chair like[13,14]" or "boat like[14]" transition state to give the Compounds **7** or **8** respectively. The biological activity of these derivatives will be published elsewhere.



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4. In the ß series the signals for OCH_2 and 10-H groups appear in upfield compared to those in the α series.

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6. Compound **3**. mp137°c, (yield 82%), M/e M^+ 322. Analysis calcd. For $C_{18}H_{26}O_5$. Calcd (Found). C,67.49(67.18),H,7.91(8.07).Proton NMR ($CDCl_3$): δ 5.56(s,1H,H_{15}),5.45(s,1H,H_{13}),5.08(t,1H,olefinic H),4.72 (t,1H,olefinic H),4.4(two d, J=7Hz,2H,H_{11}),1.42(s,3H,3-Me),1.4(s,3H, 9-Me),1.0(bd,3H,6-Me).

7. Compound **5**. Oil (yield 65%), M/e M^+ 322. Analysis cacld.For $C_{18}H_{26}O_5$ Cacld (Found). C,67.49(67.28),H,7.91(8.07). Proton NMR ($CDCl_3$): δ 5.34(s,1H,H_{15}),5.10(s,1H,H_{13}),4.9(m,1H,olefinic H),4.7(m,1H,olefinic H),4.3-4.6(m,2H,H_{11}).

8. Compound **6**. mp 125-128°c. Anal.cacld for $C_{18}H_{28}O_5$. Cacld (Found). C, 66.33(66.66),H,8.58(8.70). Proton NMR($CDCl_3$): δ 5.51(s,1H,H_{15}),5.28 (s,1H,H_{13}),4.09(t,J=8.0Hz,1H,H_{11b}),3.44(J=11.0,J=8.0Hz,1H,H_{11a}),1.36 (s,3H,3-Me),1.2(s,9-Me),0.95(bd,10-Me),0.84(bd,6-Me). NOE 9-Me ⟶13-H,H_{11a}⟶ 13Me, 9-Me,10-Me.

9. Compound **7**. mp 132-135°c, yield 30%. Analysis calcd. For $C_{18}H_{28}O_5$. Calcd (Found). C,66.33(66.50),H,8.58(8.48). Proton NMR ($CDCl_3$): δ 5.5(s,1H,H_{15}),5.3(s,1H,H_{13}),4.12(t,J=9Hz,1H,H_{11b}),3.42(dd,J=10Hz, 10Hz,1H,H_{11a}).

10. Compound **8**. mp118-120°c, yield 21%, M/e M^+ 324. Analysis cacld. For $C_{18}H_{28}O_5$. Cacld (Found). C,66.33(66.30),H,8.58(8.50).Proton NMR ($CDCl_3$): δ 5.1(s,1H,H_{15}),4.9(s,1H,H_{13}),4.12,t,1H,H_{11b}),3.48(t,1H, H_{11a}).

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