INVESTIGATION OF STEREOCHEMICAL CONTROL FOR STEROID SIDE CHAIN BY KINETIC PROTONATION OF TETRONATE DERIVATIVES+

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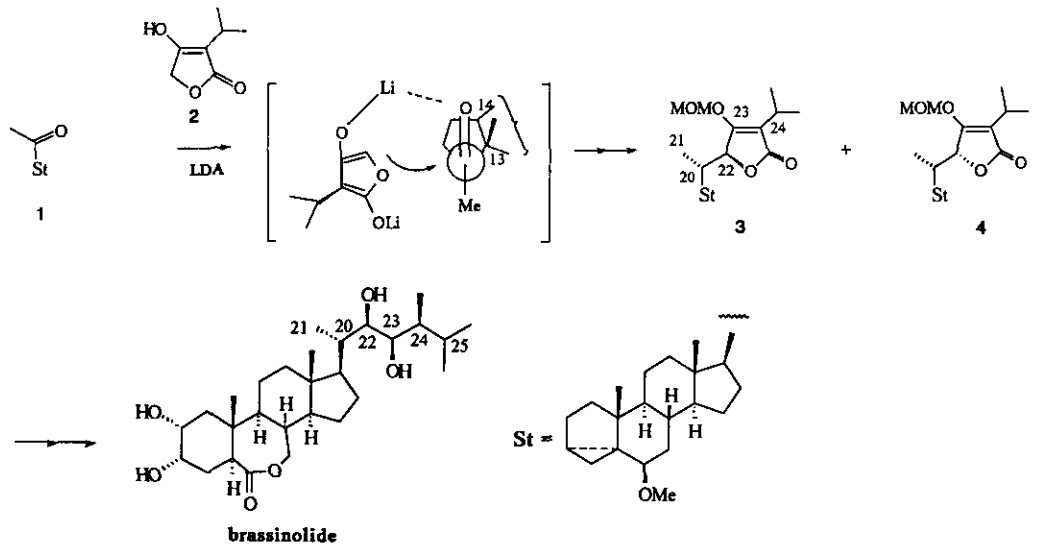
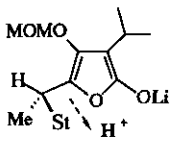
Abstract----Stereochemical control for construction of steroidal side chains by kinetic protonation of tetronate derivatives is described. Kinetic protonation of the (22R)-tetronates (4 and **11**) proceeded with the inversion of the stereochemistry at the C-22 position to afford the corresponding (22S)-tetronates (3 and **12**), whereas the same treatment of **9a** and **9b** gave only a mixture of stereoisomers. Furthermore, isomerization of the double bond of **7a** and **7b** led to the formation of (20E)-olefin(**8a**) and (20Z)-olefin (**8b**)(84:16) with moderate stereoselectivity.

Recently we have developed a stereoselective construction of poly-hydroxylated steroid side chain by utilizing tetronic acid derivatives (2) where the stereochemistry at the C-22 position was determined by chelation control, and this strategy was successfully applied to the synthesis of brassinolide,[1,2] as described in Scheme 1.



Scheme 1

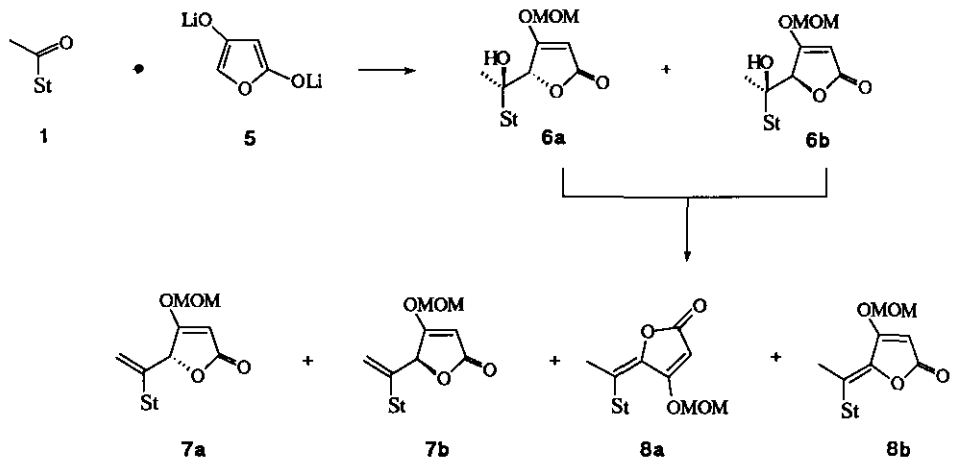
It would be presumed that (22R)-tetronate(4), the major product in the above chelation controlled synthesis, could be converted into **3** by a kinetic protonation of the enolate because of the preferable protonation from the less hindered side of the conformation **A** (Fig. 1) based on the consideration of $A^{1,3}$-strain,[3] and this isomerization procedure might provide an alternative synthetic route to ecdysone side chains stereoselectively.



A

Figure 1

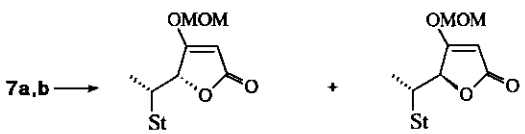
Thus, the tetronate(4) was treated with an excess of LDA in THF to generate the corresponding enolate, which on protonation with aqueous Na_2SO_4 afforded **3** with the complete inversion of the stereochemistry at the C-22 position. Whereas the same treatment of **3** gave the starting material, and these results prompted us to investigate the stereoselectivity at the C-22 position on steroid side chains employing the kinetic protonation of tetronate derivatives. Initially, we examined the kinetic protonation of the tetronates (**9** and **11**). Preparation of **11** was carried out by adopting the procedure developed by us.[1] Addition reaction of the dianion (5)(prepared from tetronic acid and 2.2 equiv. of LDA at -78 °C in dry THF) to the 20-oxosteroid (**1**)



Scheme 2

followed by treatment of the adducts with chloromethyl methyl ether afforded the MOM ethers (**6a** and **6b**) (77 % yield) as an inseparable mixture in a ratio of 76 : 24,[4] respectively. Dehydration of the tertiary alcohols (**6a** and **6b**) was achieved by treatment with thionyl chloride and pyridine to produce the exo-olefins (**7a** and **7b**) (36 % yield) as an inseparable mixture in a ratio of 76 : 24 [4] together with the endo-olefins (**8a** and **8b**) (68 : 32,[4] 36 % yield)(Scheme 2).

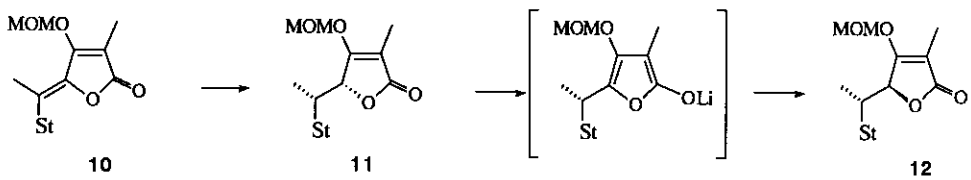
Hydrogenation of the exo-olefins (**7a** and **7b**) over platinum oxide in ethyl acetate under medium pressure (7 atm) of hydrogen furnished the tetronates (**9a** and **9b**)(92 % yield) as inseparable diastereoisomers at the C-22 position in a ratio of 76:24.[4] A mixture of the requisite tetronates (**9a** and **9b**) obtained above was then subjected to the kinetic protonation under the above reaction conditions, however the expected selectivity was not observed unfortunately to give **9a** and **9b** in almost the same ratio (62:38)[4] as that of the starting material (Scheme 3).



9a **9b**

Scheme 3

On the other hand, kinetic protonation of the (22R)-tetronate(11), obtained by hydrogenation of 10,[1b] proceeded with moderate diastereoselectivity to afford **12** predominantly together with **11** (75:25,[4] 88 % yield) (Scheme 4).

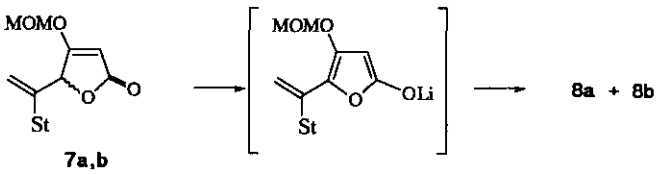


10 **11** **12**

Scheme 4

These results indicated that α-substituent on the tetronate would play an important role in the kinetic protonation of the tetronate, and also the stereochemical control at the C-22 position could be achieved by the application of this strategy to the tetronate having a relatively bulky

α-substituent. When this protonation was applied to the trienolates derived from a mixture of **7a** and **7b** (76:24), a mixture of (20E)-olefin (**8a**) and (20Z)-olefin (**8b**) was isolated in a ratio of 84:16[4] in 68.4 % yield (Scheme 5).

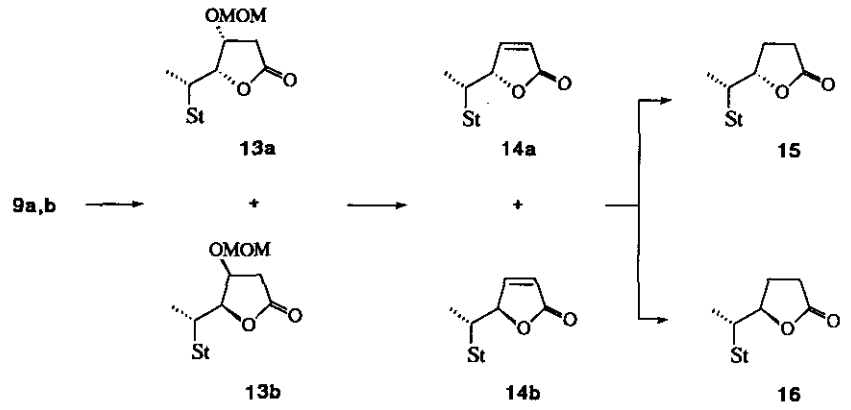


Scheme 5

Interestingly, treatment of **7a** and **7b** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene afforded **8a** and **8b** in the same ratio as above,[4] in 80 % yield. The preferential formation of E-isomer could be rationalized by assuming that this isomerization occurred via the energetically more favoured s-trans conformation **B** than the s-cis isomer **C**[5] (Fig. 2).

Figure 2

In order to determine the stereochemistry at the C-22 position unambiguously, compounds (**9a** and **9b**) were further converted into the known γ-lactones (**15** and **16**).[6] Hydrogenation of a mixture of the tetronates (**9a** and **9b**) over rhodium on alumina under 7 atm of hydrogen in ethyl acetate afforded the lactones (**13a** and **13b**) as an inseparable mixture in a ratio of 78 : 22[4] in 90% yield, which were then subjected to the elimination of the MOM ethers by treatment with an excess of lithium cyclohexylisopropylamide in dry THF at 0°C to give the butenolides (**14a** and **14b**). Finally the hydrogenation of a mixture of **14a** and **14b** over rhodium on alumina under 7 atm of hydrogen in ethyl acetate furnished the lactones (**15** and **16**) in 67.6 and 21.4 % yields, respectively (Scheme 6).



Scheme 6

Further investigations of stereochemical control for construction of steroidal side chains by the kinetic protonation of the tetronate derivatives including the conformational analysis of the reaction are currently in progress.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

+ Dedicated to the memory of the late Professor Tetsuji Kametani.

1 a) T.Kametani, T.Katoh, M.Tsubuki, and T.Honda, J.Am.Chem.Soc., 1986,**108**, 7055; b) T.Kametani, T.Katoh, M.Tsubuki, and T.Honda, Chem.Pharm.Bull., 1987, **35**, 2334; c) T.Kametani, T.Katoh, J.Fujio, I.Nogiwa, M.Tsubuki, and T.Honda,J.Org.Chem.,1988,53,1982.

2 For several stereocontrolled syntheses of 22-hydroxysteroids see: B.M.Trost and Y.Matsumura,J.Org.Chem., 1977, **42**, 2036; M.M.Midland and Y.C.Kwon, J.Am.Chem.Soc., 1983, **105**, 3725; E.Nakamura and I.Kuwajima, J.Am.Chem.Soc., 1985, **107**, 2138; T.Kametani, M.Tsubuki, K.Higurashi, and T.Honda, J.Org.Chem., 1986, 51, 2935; M.Koreeda and D.J.Ricca, J.Org.Chem.,1986, **51**, 4090; Y.Yamamoto, S.Nishii, and J.Yamada, J.Am.

Chem.Soc.,1986,**108**, 7116; K.Mikami,T.P.Loh, and T.Nakai, J.Chem.Soc., Chem.Commun.,1988,1430.

3 F.Johnson,Chem.Rev., 1968,**68**,375; K.Tomioka, K.Yasuda, H.Kawasaki, and K.Koga, Tetrahedron Lett.,1986,**27**,3247.

4 The ratios of the products were determined by 270 MHz ^{1}H-nmr analyses of the mixtures.

5 M.E.Squillacote, R.S.Sheridan, O.L.Chapman, and F.A.L.Anet, J.Am. Chem.Soc.,1979,**101**,3657.

6 T.Kametani, T.Katoh, M.Tsubuki, and T.Honda, Chem.Lett., 1985, 485.

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