Pergamon

Tetrahedron Letters, Vol. 35, No. 47, pp. 8735-8738, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01948-7

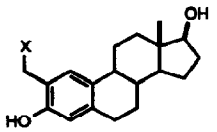
SYNTHESIS OF 2-SUBSTITUTED HYDROXYALKYL AND AMINOALKYL ESTRADIOLS

Carl J. Lovely and Robert W. Brueggemeier*
College of Pharmacy, The Ohio State University, 500 West 12th Avenue, Columbus, Ohio, 43210, USA

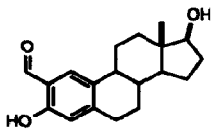
Abstract: An homologous series of 2-substituted hydroxyalkyl and aminoalkyl estradiols have been prepared by elaboration of the formylated estradiol derivative **10**.

Keywords: Breast cancer, 2-substituted estradiol, 2,4-hydroxylase

Estrogens play a pivotal role in around 50-60% of breast cancer cases.[1,2] Understanding the roles of estradiol and its metabolites (catechol estradiols) in breast tumor initiation and development may provide useful therapies for breast cancer treatment in the future. As part of a program directed towards these ends we required a number of 2-substituted catechol estradiol mimics **1-6** to study estrogen receptor affinities, gene expression of estrogen induced responses, inhibition of 2- and 4-hydroxylases and cell growth .



1; X=OH, **2**: X=NH_2, **3**: X=CH_2OH, **4**: X=CH_2NH_2, **5**: X=CH_2CH_2OH, **6**: X=$CH_2CH_2NH_2$



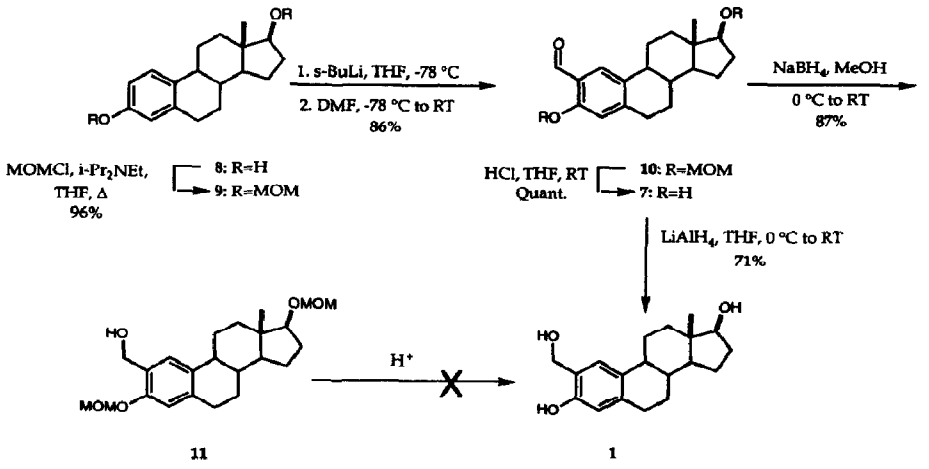
7

The aminoethyl derivative **4** has been prepared previously; however, the route was low yielding and was not suitable for the preparation of other derivatives.[3] We required a route that was flexible enough to provide access to all the desired targets. A survey of the literature revealed that formyl estradiol **7** had been prepared earlier *via ortho* lithiation of a protected estradiol derivative **9**.[4] This compound appeared to be an ideal starting point for the synthetic work described in this letter.

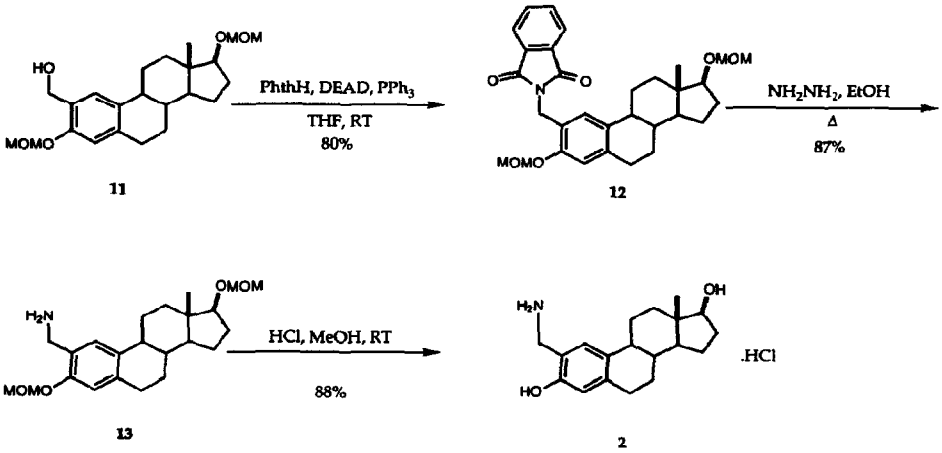
The synthesis commenced by protecting estradiol with MOMCl by a modification of the general procedure of Stork and Takahashi to give **9**.[5] Deprotonation of **9** with *s*-BuLi, followed by the addition of freshly distilled DMF (from CaH_2) gave **10** exclusively in 86% yield. None of the regioisomeric 4-substituted

compound was isolated. Deprotection with dilute HCl and subsequent $LiAlH_4$ reduction gave the desired triol **1**. $NaBH_4$ reduction of **10** gave **11**,[6] which upon treatment with phthalimide under Mitsunobu conditions gave **12**.[7] Phthalimide cleavage with hydrazine followed by simultaneous deprotection and salt formation with methanolic HCl gave **2**.

Scheme 1



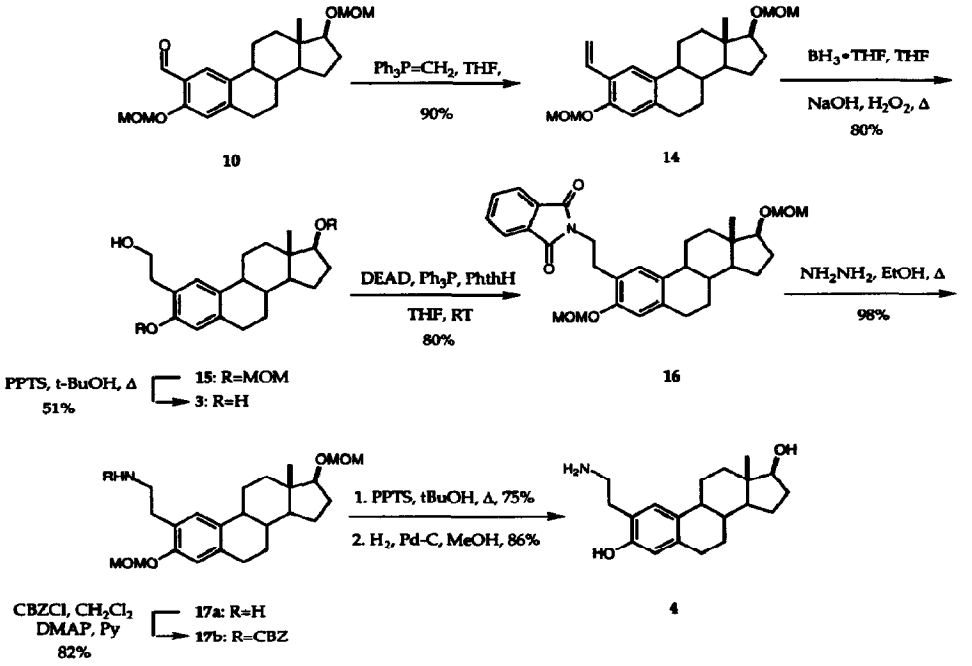
Scheme 2



Attempted preparation of the ethyl and propyl derivatives by condensation of the organolithium species, generated from **9** and *s*-BuLi, with suitable two- and three-carbon electrophiles was unsuccessful. Other homologation strategies, for example, conversion of benzyl alcohol **11** into the benzylnitrile derivative, *via* mesylation and reaction with NaCN, were not satisfactory due to problems encountered during subsequent elaborations. The use of phosphorus stabilized anions proved more successful. Thus, Wittig methylenation of **10** with $Ph_3P{=}CH_2$ gave the terminal olefin **14**. Hydroboration of **14** followed by an oxidative work up gave the ethyl alcohol **15**. Deprotection of **15** with PPTS in refluxing t-BuOH then gave **3**.[8] Target amine **4** was

prepared *via* phthalimidoylation of ethyl alcohol **15**. Thus **15** was treated with phthalimide using Mitsunobu conditions to give **16**. Hydrazinolysis of **16** gave the amine **17a**, which was protected with CBZCl to aid purification. The MOM protecting groups were removed next by acidic hydrolysis (PPTS, t-BuOH, Δ), followed by reductive cleavage of the carboxybenzyl protecting group by catalytic hydrogenation.

Scheme 3

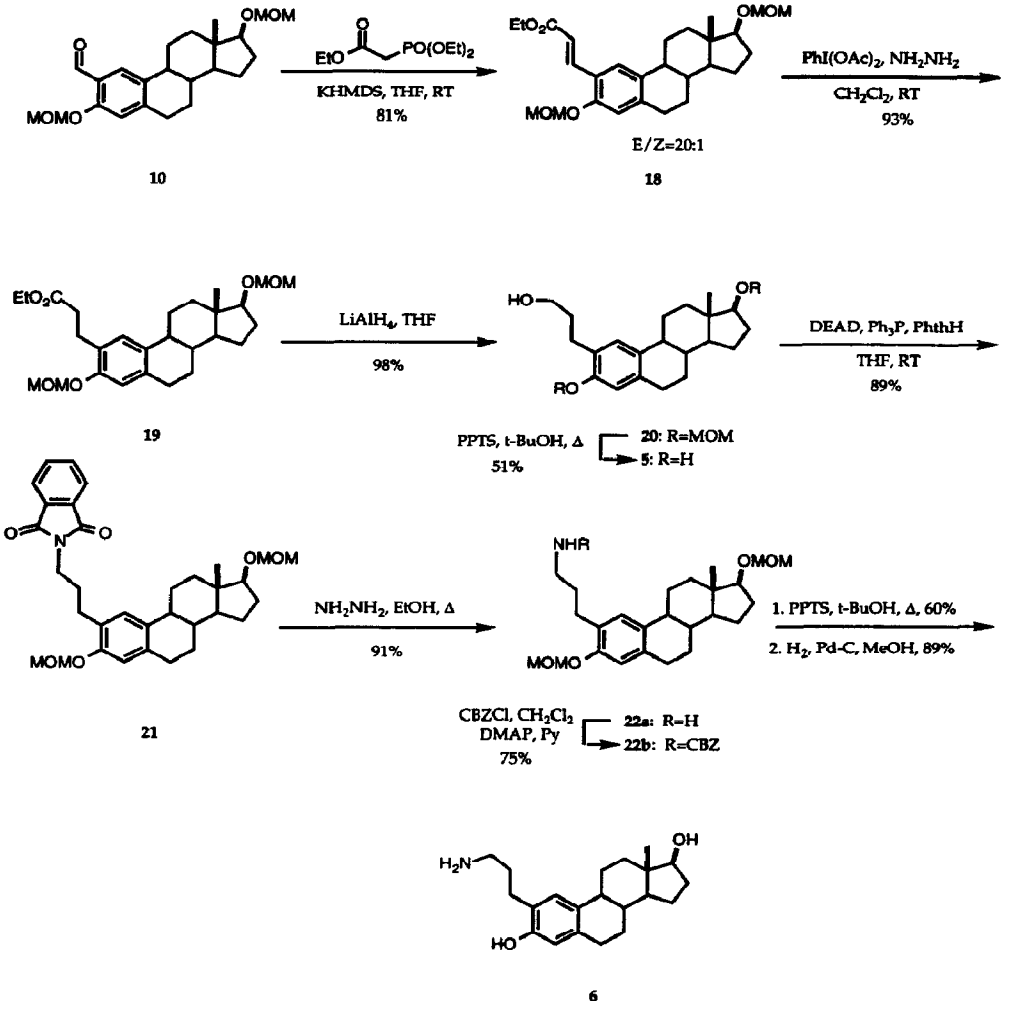


The propyl derivatives were prepared by means of a Horner-Wadsworth-Emmons reaction with triethylphosphonoacetate and **10** to give the cinnamate ester **18** (>20:1 E/Z). Attempted reduction of **18** with H_2/Pd-C or $NaBH_4$ were unsuccessful, however reduction with diimide, generated in situ by oxidation of hydrazine with iodobenzene diacetate, gave the dihydrocinnamate **19**.[9] Further reduction of the ester with $LiAlH_4$ gave the propyl alcohol **20**. Acid treatment (PPTS, t-BuOH, Δ) of **20** gave the desired triol **5** in 51% yield. Reaction of **20** with phthalimide under Mitsunobu conditions gave **21**. Phthalimide cleavage with hydrazine and protection with CBZCl gave **22b**. The deprotection protocol as used for the ethylamine **4** gave the desired propylamine **6**.

Compounds **1-7** are currently being evaluated *in vitro*, the results emerging from these studies will be published elsewhere.

Acknowledgments: This work was supported in part by the NIH CA 58003.

Scheme 4



References

1. Cancer Facts and Figures, 1993, American Cancer Society Publication.
2. McCarty, Jr., K.S.; McCarty, Sr., K.S. in Regulatory Mechanisms in Breast Cancer (eds. Lipmann, M. and Dickson, R.), Kluwer Academic Publishers, Boston, 1991, Ch 9.
3. Stevens, J.M., PhD Dissertation, The Ohio State University, 1988.
4. Pert, D.J.; Ridley, D.D., *Aust. J. Chem.*, **1987**, *40*, 303; Pert, D.J.; Ridley, D.D., *Aust. J. Chem.*, **1989**,*42*, 405.
5. Stork, G.; Takahashi, T., *J. Am. Chem. Soc.*, **1977**, *99*, 1275.
6. Attempted acidic hydrolysis of **11** with HCl or PPTS led predominantly to decomposition
7. Hughes, D.L., *Org. Reactions*, **1992**, *42*, 656.
8. Monti, H.; Leandri, G.; Klos-Ringuet, M.; Corriol, C., *Synth. Commun.*, **1983**, *12*, 1021.
9. Moriarty, R.M.; Vaid, R.K.; Duncan, M.P., *Synth. Commun.*, **1987**, *17*, 703.

(*Received in USA* 10 *August* 1994; *revised* 20 *September* 1994; *accepted* 26 *September* 1994)