Pergamon

Tetrahedron Letters 41 (2000) 3295–3298

TETRAHEDRON LETTERS

Synthesis of lipidic tamoxifen

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Received 17 August 1999; accepted 7 March 2000

Abstract

We describe a general method for elaboration of the ethyl sidechain of tamoxifen and its primary 4-hydroxy metabolite. Novel lipidic tamoxifen and a functionalized B-ring analog were synthesized from a common stilbene oxide intermediate for potential liposomal applications including estrogen receptor targeting.

It is estimated that approximately one in nine women will develop breast cancer, the most common form of malignancy in women.[1] Early detection and imaging is paramount to effectively staging and treating this disease.[2] Much current research to improve early detection of breast cancer seeks to utilize radiolabeled tamoxifen (**1**) or radiolabeled tamoxifen analogs for imaging estrogen receptor (ER) positive breast cancer.[3] Studies have shown that tamoxifen is a highly effective antagonist of the ER and, consequently, tamoxifen is currently the most widely used adjuvant drug therapy for the treatment of ER-positive breast cancer.[4] The prevalence of estrogen receptors in the majority of breast tumors also provides a means of imaging these tumors. Indeed, tamoxifen-based radiopharmaceuticals containing ^{18}F, ^{111}In, or ^{131}I have been employed for this task.[5] Although these agents successfully image the target tissue, the short half life of ^{18}F and the requirement of expensive particle accelerators have limited widespread application of this strategy. Magnetic resonance (MR) imaging using an ER-targeted approach to improve conspicuity remains to be explored and might offer a more practical and less expensive alternative to the use of radiopharmaceuticals. We envision that incorporation of a tamoxifen-linked lipid into lamellae of liposomal MRI preparations[6] potentially could improve imaging in ER-rich tissues.[7] We report herein a general method for attaching a lipid domain onto the ethyl sidechain of both tamoxifen and its more active[8] 4-hydroxy metabolite (**2**). The rationale for extending the ethyl sidechain relies on observations made by Podoloff et al.[5b] who demonstrated that derivatization at this site did not significantly interfere with recognition by the ER.[9] The synthesis of representative lipidic tamoxifen derivatives **3** and **4** is conveniently achieved from the common epoxide intermediate **5**, a novel substrate for tamoxifen derivatization.

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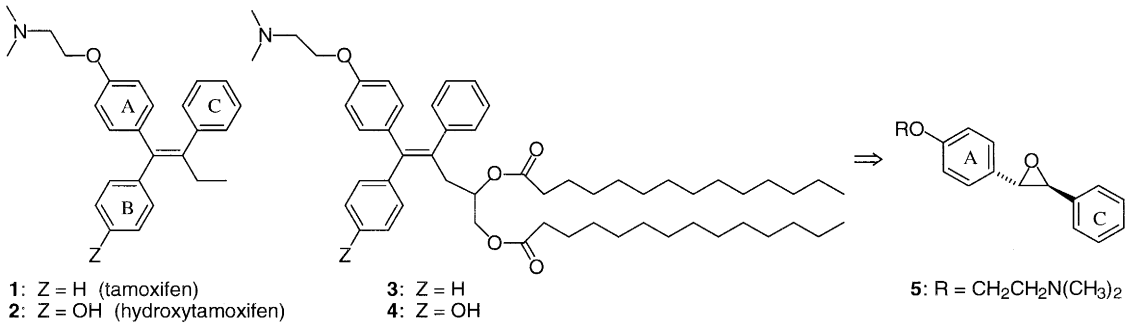
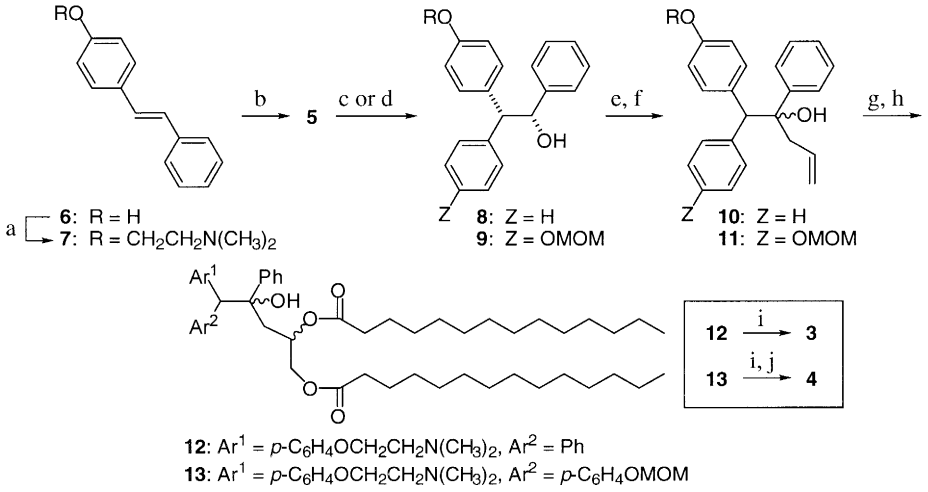
0040-4039/00/$ - see front matter
PII: S0040-4039(00)00421-4



Alkylation of *trans*-4-hydroxystilbene (**6**) with *N*,*N*-dimethylaminoethyl chloride readily provided amine **7** (Scheme 1). To avoid amine oxidation, the epoxidation of **7** was conducted via bromohydrin formation[10] followed by treatment with base to obtain epoxide **5**.[11] Introduction of the tamoxifen and hydroxytamoxifen B-ring was achieved by copper(I)-catalyzed reaction of **5** with either PhMgBr or the Grignard reagent derived from (methoxymethyl)-protected 4-bromophenol, respectively. As predicted,[12] epoxide cleavage proceeded regioselectively at the electron rich benzylic position to deliver tamoxifen precursor **8** and the *p*-(methoxymethoxy) derivative **9** in good yields. Swern oxidations of **8** and **9** proceeded smoothly to afford the corresponding phenyl ketones in 75 and 80% yield, respectively. Treatment of the ketones with allylmagnesium chloride in THF failed to deliver 1,2-addition products, giving instead predominantly reduction products (e.g. **8** and **9**, and their diastereomers). However, a change in solvent to Et_2O facilitated addition of the Grignard reagent to give allylic alcohols **10** and **11** as a mixture of diastereomers in 70 and 87% yield, respectively. The osmylation of alcohol **10** using standard conditions[13] gave a mixture of the corresponding diastereomeric triols, and subsequent bisacylation using excess myristoyl chloride gave the alcohol diester **12** in 61% yield for the two steps. Treatment of **11**



Scheme 1. (a) $(CH_3)_2NCH_2CH_2Cl{\cdot}HCl$, DMF, KOH, 25°C, 12 h, 97%; (b) (i) NBS (2 equiv.), H_2O (2 equiv.), DMSO, 10°C, 0.5 h; (ii) aq. KOH, rt, 0.5 h, 54%; (c) PhMgBr (4 equiv.), CuI (0.2 equiv.), −40°C, 10 min, then **5**, −40°C to rt, 12 h, 84%; (d) *p*-$(CH_3OCH_2O)C_6H_4MgBr$ (4 equiv.), CuI (0.2 equiv.), −40°C, 10 min, then **5**, −40°C to rt, 12 h, 82%; (e) (i) $(CO)_2Cl_2$, DMSO, CH_2Cl_2, −78°C; (ii) Et_3N, −78°C to 0°C; (f) CH_2CHCH_2MgCl (4 equiv.), Et_2O, −50°C to rt, 12 h; (g) acetone:H_2O (8:1), cat. OsO_4, NMO, rt; (h) $ClC(O)CH_2(CH_2)_{12}CH_3$ (2.1 equiv.), CH_2Cl_2, TEA, DMAP, 0°C to rt, 12 h; (i) pyridine, $SOCl_2$, −10°C, 3 h; (j) TFA (30 equiv.), anisole (30 equiv.), CH_2Cl_2, rt, 12 h, 80%

under similar conditions gave the MOM-protected analog **13** in 64% yield. The tamoxifen core was established by alcohol dehydration of **12** using thionyl chloride in pyridine to give lipidic tamoxifen **3** as a 1:1 *E*:*Z* mixture in 70% yield.[14] Separation of the isomers is not critical for application in targeted imaging since both isomers of tamoxifen exhibit the desired ER specificity.[15,16] Dehydration of **13** using identical conditions followed by MOM ether cleavage using a 1:1 trifluoroacetic acid–anisole mixture[17] gave lipidic hydroxytamoxifen derivative **4** in a 64% two-step yield.[18] Other methods of MOM-group deprotection were attempted at this and earlier stages in the synthesis, but none were as effective as the anisole-mediated method used here. By analogy to hydroxytamoxifen (**2**), equilibration of the *E*:*Z* stereoisomers in lipidic analog **4** is expected to readily occur in vivo making the mixture potentially suitable for targeted imaging applications.[19]

In conclusion, we have developed a general synthesis of lipidic tamoxifen and hydroxytamoxifen analogs from a common epoxide intermediate that serves as a template for straightforward derivatization of the B-ring and ethyl sidechain domains.[20,21]

Acknowledgements

This work was supported by the University of California Cancer Research Coordinating Committee.

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14. Compound **3**: colorless oil; ^{1}H NMR (CD_3Cl) δ 0.87 (m, 6H), 1.23–1.27 (m, 40H), 1.51 (m, 4H), 1.99 (m, 1H), 2.08 (m, 1H), 2.21 (m, 4H), 2.93 (s, 6H), 3.49 (m, 2H), 3.90 (m, 1H), 4.14 (m, 1H), 4.51 (m, 2H), 5.09 (m, 1H), 6.79–7.50 (m, 14H); ^{13}C NMR (CD_3Cl) δ 14.1, 22.7, 24.8, 29.1 (2), 29.3 (3), 29.5, 29.6 (2), 29.7, 31.9, 34.0, 36.5, 43.8, 56.6, 62.8, 64.9, 70.3, 114.1 (2), 114.3, 125.6, 126.1, 126.6, 127.3, 127.4, 127.5, 128.0 (2), 129.5, 130.5, 131.0, 135.5, 136.6, 141.1, 141.5, 142.5, 155.9, 172.8, 173.4.

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18. Compound **4** (1:1 *E*:*Z* mixture): colorless oil; ^{1}H NMR (CD_3Cl) δ 0.88 (m, 12H), 1.22–1.26 (m, 80H), 1.50–1.53 (m, 8H), 2.00 (m, 4H), 2.00–2.18 (m, 4H), 2.20–2.28 (m, 8H), 2.35 (s, 6H), 2.46 (s, 6H), 2.74 (m, 2H), 2.85 (m, 2H), 3.88 (m, 2H), 4.06 (m, 2H), 5.06 (m, 2H), 6.33 (d, 4H), 6.44 (d, 4H), 6.65–7.15 (m, 20H); ^{13}C NMR (CD_3Cl) δ 14.1, 22.7, 24.8, 29.1, 29.3 (2), 29.4, 29.5, 29.6, 31.9, 34.0, 44.8, 44.9, 57.6, 64.0, 64.5, 64.8, 70.5, 113.0, 113.9, 114.6, 115.4, 126.2, 128.0, 128.4, 129.6, 130.7, 130.8, 131.7, 131.9, 134.4, 141.5, 141.7, 142.5, 156.0, 172.8, 173.5.
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