Tetrahedron Letters 53 (2012) 3633–3636

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Total synthesis of the aromatase inhibitor dihydroisocoumarin via protective opening of lactones

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ARTICLE INFO

Article history:
Received 31 March 2012
Revised 30 April 2012
Accepted 3 May 2012
Available online 11 May 2012

Keywords:
Xyris pterygoblephara
Dihydroisocoumarin
Wittig
Grubbs cross metathesis
Sharpless dihydroxylation and lactonization

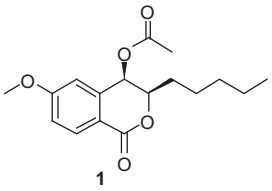
ABSTRACT

Asymmetric total synthesis of a dihydroisocoumarin, (3*R*,4*R*)-(−)-6-methoxy-1-oxo-3-pentyl-3,4-dihydro-1*H*-isochromen-4-yl acetate (**1**) starting from commercially available *m*-anisic acid is described. Herein, we depict the use of protective opening of lactones and construction of δ lactone. The synthesis involves Wittig, Grubbs cross metathesis, and Sharpless dihydroxylation reactions.

Cancer chemotherapy relies on therapeutic agents with cytotoxic properties that inhibit tumor cell proliferation and cause cell death. Aromatase inhibitors have shown improved efficacy and reduced side effects against advanced and early stage breast cancer in comparison with the estrogen antagonist tamoxifen.[1–4] The process of drug discovery through the use of small-molecule natural products is well established.[5] In some illustrations, the natural products themselves are developed and recorded as medicines[6] and help as a guide for medicinal chemistry investigations and to find final drugs.[7–10]

In the anticancer drug discovery, the coumarin functionality is an important feature for anticancer agents.[11–13] The tenacity needed to preserve the configuration and functionality of drugs from natural products call for estimable efforts and skills toward their synthesis in enantiomerically pure form.[14]

The dihydroisocoumarin, (3*R*,4*R*)-(−)-6-methoxy-1-oxo-3-pentyl-3,4-dihydro-1*H*-isochromen-4-yl acetate (**1**) was isolated from aerial parts of *Xyris pterygoblephara*,[15] showed aromatase inhibitory activity at concentration[16] of $IC_{50} = 1.6 \pm 0.1$ μM and was active against dermatophytic fungi.[15] For the past several years we have been engaged in the total synthesis of biologically active natural products by using natural and commercial available sources.[18] We now report our latest efforts at expanding the scope of the synthetic utility for the conversion of γ-lactone into δ lactone. In this context, the potent biological activities and the structural features of dihydroisocoumarin (**1**) have inspired us to pursue stereoselective synthesis that would provide a basis for suitable derivatizations and allow further biological evaluations. Total synthesis of compound **1** was already at an advanced stage,[17] but different from ours.



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The retro synthetic analysis of the dihydroisocoumarin (**1**) is depicted in Scheme 1. We envisaged that protective opening of five membered lactone **18** exposed to acetyl chloride would give target molecule **1**, which in turn could be obtained from *E*-olefin **10** by employing Sharpless asymmetric dihydroxylation followed by lactonization as key steps.

E-Olefin **10** can be derived from acid **4** using Wittig homologation and Grubbs cross metathesis sequentially, which could be furnished from **2** via protective opening of phthalide. The synthesis was commenced from the commercially available *m*-methoxybenzoic acid **2** (Scheme 2), which was converted into phthalide **3** following the literature procedure.[19] The lactone ring in compound **3** was opened with methanol[20] in the presence of K_2CO_3 to obtain potassium salt of the acid, which was protected with benzyl bromide in the presence of NaH to form the compound **4**. The acid group in **4** was converted into alcohol **5** by the reduction with LAH, followed by the

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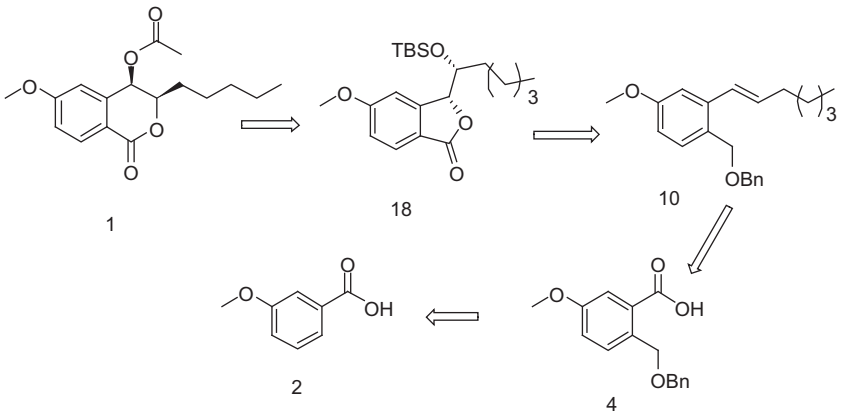
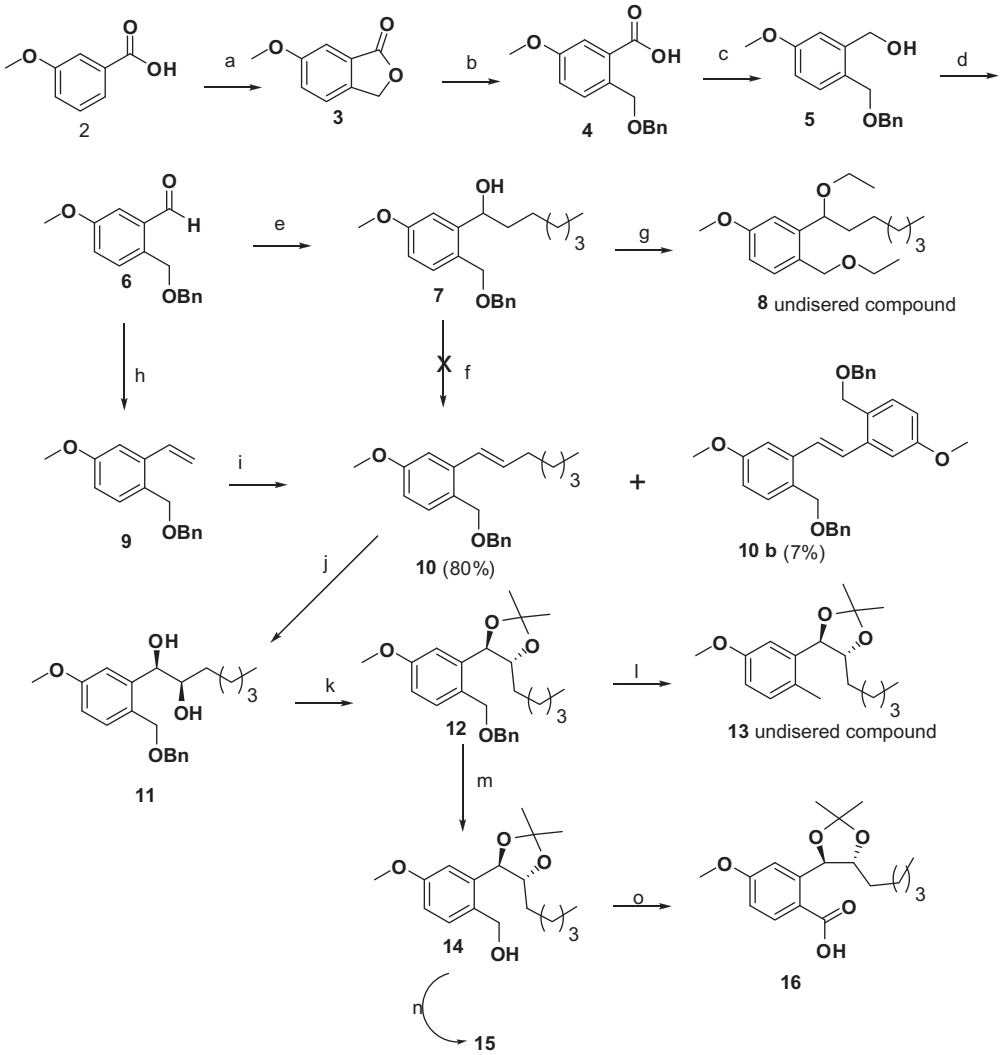
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.05.012

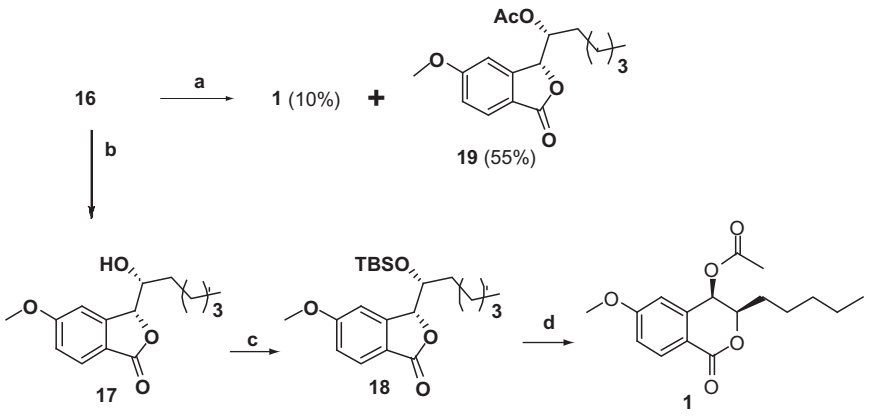


Scheme 1. Retrosynthetic analysis of dihydroisocoumarin (**1**).



Scheme 2. Reagents and conditions: (a) CH_2O, Glacial acetic acid, 11 N HCl, reflux, 1 h, 75%; (b) (i) methanol, K_2CO_3, reflux 3 h; (ii) NaH, benzyl bromide, 4 h, over two steps 84%; (c) LAH, THF 1 h, 90%; (d) $(COCl)_2$, DMSO, triethylamine, −78 °C, 1 h, 95%; (e) 1-bromo hexane, Mg, THF, 0 °C, 3 h, 89%; (f) *P*TSA, THF reflux; (g) 11 N HCl, ethanol, reflux, 75%; (h) *t*-BuOK, $PPh_3PCH_3^+Br$, THF, −10 °C, 4 h, 80%; (i) Grubbs 2nd generation catalyst (10 mol %), DCM, reflux, 12 h, 80%; (j) AD-mix-β, $CH_3SO_3NH_2$, *t*-butanol/H_2O (1:1), 0 °C, 24 h, 95%; (k) 2,2 DMP, *P*TSA, DCM, rt, 5 h, 95%; (l) Pd/C, H_2, ethylacetate, reflux, 5 h, 95%; (m) Raney-Nickel, H_2, ethanol, rt, 48 h, 95%; (n) $(COCl)_2$, DMSO, triethylamine −78 °C 1 h, 95%; (o) $NaClO_2$, NaH_2PO_4, *t*-Butanol/H_2O (7:3), rt, 8 h, 94%.

Swern oxidation to afford aldehyde **6**. The aldehyde **6** was subjected to Grignard reaction with hexylmagnesium bromide to afford the secondary benzyl alcohol **7** in 89% yield. Dehydration of secondary alcohol **7** to compound **10** was unsuccessful with various reagents



Scheme 3. Reagents and conditions: (a) $FeCl_3$, acetyl acetone, toluene, reflux, 24 h, 65%; (b) HCl, methanol, rt, 93%; (c) TBSCl, imidizole, rt, 3 h, 93%; (d) (i) K_2CO_3, methanol, reflux 3 h; (ii) THF/acetyl chloride 8 h; (iii) HCl, methanol, rt, overall yield 70%.

such as *p*-TSA in dry THF at reflux condition,[18e] dehydromesylation[21], and dehydrohalozenation.[22] Interestingly, when compound **7** reacted with 11 N HCl in ethanol,[23] it afforded undesired compound **8.** The attempts were therefore abandoned. Then, to overcome the first impediment toward the synthesis of **1**, the aldehyde **6** was converted into the terminal alkene **9** using Wittig reaction with methyltriphenylphosphonium bromide salt in the presence of *tert*-BuOK, which was subjected to cross metathesis reaction[24] with 1-heptene by using Grubbs 2nd generation catalyst in CH_2Cl_2 to afford the *E*-olefin **10** along with by product **10b** (*trans* dimer of **9**). *E*-Olefin **10** was subjected to Sharpless dihydroxylation[25] with β-AD-mix to afford **11** in 95% yield, which was modified as an acetonide compound **12** with 2, 2 DMP in dry DCM and *p*-TSA as catalyst.

The removal of benzyl protecting group in compound **12** was unsuccessful to give alcohol **14**, with Li/naphthalene reaction. When compound **12** was subjected to hydrogenation in the presence of palladium catalysts like palladium(II) acetate, palladium hydroxide, and palladium–carbon in various solvents (ethyl acetate, ethanol and methanol) at either reflux or room temperature conditions at hydrogen atmosphere afforded compound **13**. Compound **12** was subjected to hydrogenation in the presence of Raney nickel in ethanol at reflux condition also yielded compound **13** but, fortunately at room temperature afforded alcohol **14**. Thus, alcohol **14** was oxidized to aldehyde **15** using IBX in DMSO, which was immediately further oxidized to acid **16** by treating with $NaClO_2$/NaH_2PO_4.

At this juncture, target molecule **1** was obtained from acid **16**, via a tandem deacetonide/aceylation, using $FeCl_3$ and acetyl acetone in benzene at reflux.[26] Although, the tandem reaction occurred, the yield of the desired compound **1** only 10% and the major product **19** in 55% yield was obtained (Scheme 3). Increase in the dilution and time of addition did not give compound **1** as major product. In a different route, the acid **16** was converted into lactone **17** by using HCl in methanol. The reactive secondary hydroxyl group in lactone **17** was temporarily protected as TBS ether **18**. Now, in sequential reactions lactone opening, acetylation, and re-lactonization of **18** were carried out in three-step-one-pot fashion without isolation of intermediates to obtain compound **1** (Scheme 3). Accordingly, the TBS ether **18** was reacted with K_2CO_3 in methanol, followed by reaction with acetyl chloride in THF and finally reaction with HCl in methanol afforded compound **1** in 70% yield. The physical {$[\alpha]_D^{25}$ −65 (*c* 0.033, $CHCl_3$)} and spectroscopic data were found to be identical with the reported natural product.[16]

In conclusion, we have reported the total synthesis of the biologically active dihydroisocoumarin (**1**) with 92.4 (ee), with overall 16% yield and very high selectivity has been observed in the construction of the six membered lactone.

Acknowledgments

The authors D.C., C.B.R., D.R., and K.R. are thankful to the UGC and CSIR, New Delhi for the financial support and thankful to the Director J. S. Yadav, IICT for his constant encouragement.

Supplementary data

Supplementary data (experimental procedures and data for representative new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.012.

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