Tetrahedron Letters 52 (2011) 4137–4139

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A stereoselective synthesis of the allo-bile acids from the 5β-isomers

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ARTICLE INFO

Article history:
Received 13 April 2011
Revised 25 May 2011
Accepted 27 May 2011
Available online 27 June 2011

Keywords:
Bile acid
Allo bile acid
Selective oxidation
IBX
Lithium–ammonia reduction

ABSTRACT

The allo-bile acids are a subset of the family of steroidal detergents found in most vertebrates. Because there are no major biological feedstocks for isolation of the allo-bile acids, they must be synthesized from the abundant 5β-reduced isomers. Here we report a general set of methods for the synthesis of allo-bile acids from the corresponding 5-β isomers demarcated by a selective C-3 oxidation, IBX unsaturation, and stereoselective saturation.

Bile acids are ubiquitous small molecules across vertebrates that facilitate digestion by acting as surfactants in the lumen of the small intestine. The allo bile acids represent a subfamily of this class of physiologic molecules that is primarily demarcated by an AB-trans ring fusion (also referred to as 5α-reduced see Fig. 1). They occur widely in lower vertebrates, including various fish, birds and reptiles, but are also found sporadically in higher vertebrates and mammals, including humans.[1] Since the identification of the farnesoid X receptor (FXR) as an endogenous nuclear receptor for the bile acids,[2] there has been renewed interest in this class of physiologic molecules, and given the central role of 5α-reduced C_{24} cholanic acids in gaining access to a major subset of these bile acids, efficient methods for their synthesis will always represent important research tools.

No significant biological feedstocks are currently available that are rich in 5α-reduced bile acids. Consequently, the primary route for access to these molecules has been via chemical synthesis. To this point, since the identification of allo-cholic acid by Anderson and Haslewood in 1962,[3] several syntheses have been reported.[3–8] Our laboratory has recently become interested in studying the allo-bile acids in the context of their ability to modulate cellular signaling through FXR. After analyzing the literature we came to the conclusion that the available methods are not general across the spectrum of allo bile acids, and would further preclude access to select members of the allo-family. Further, recent reports suffer from iterative protection–deprotection, and non-selective substitution–elimination reactions.[7]

Conversely, the approach reported here can be applied across the bile acid spectrum, and is highly efficient. As shown in Scheme 1, our synthesis begins with a regioselective C-3 oxidation of methylated 5β-reduced bile acids using Ag_2CO_3 adsorbed on Celite.[9] The selective nature of this reaction is most likely due to relative steric accessibility of the C-3 position interacting with the Celite solid surface. Subsequently, any additional hydroxyl groups are protected as methoxymethyl ethers.[10] 2-Iodoxybenzoic acid (IBX) smoothly and regioselectively performs the dehydrogenation to give the Δ^4 enone.[11]

Stereochemistry of a lithium–ammonia reduction of the Δ^4 moiety proceeds as expected based on the model put forth by Stork whereby the radical anion intermediate protonates axially.[12] From a technical point of view, achieving correct stoichiometry in the lithium–ammonia reduction is absolutely crucial for success. Excess lithium will readily reduce the C-24 ester in addition to the C-3 carbonyl. In this molecule, the sequence of reactivity toward the lithium–ammonia reduction proved to be Δ^4 enone, C-24 ester, C-24 aldehyde (from the C-24 ester), and finally the C-3 ketone. If the amount of lithium is strictly controlled it is possible to obtain any of the sequential intermediates, though for this

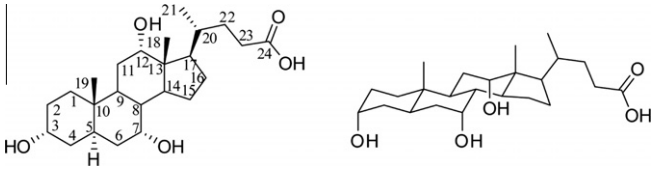

Figure 1. Numbered and 3-D representation of allo-cholic acid.

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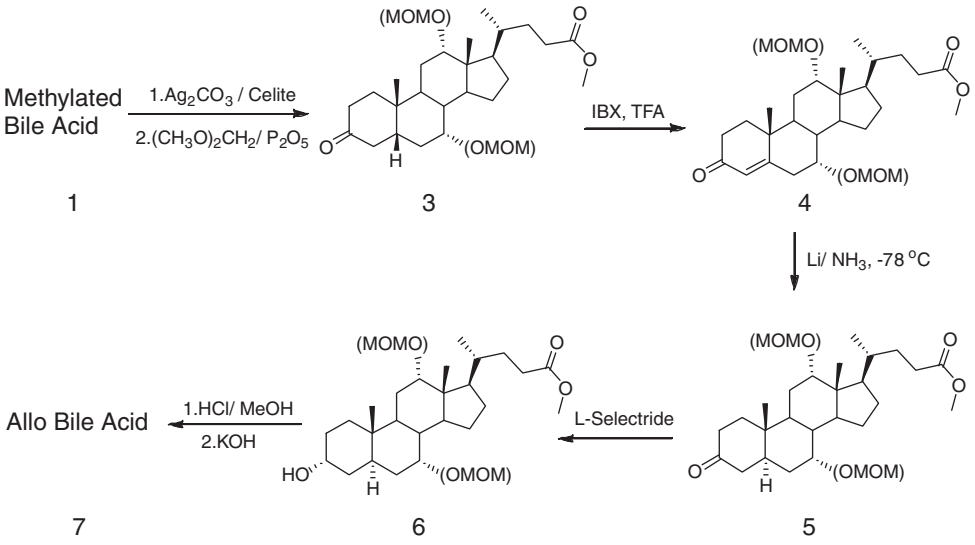
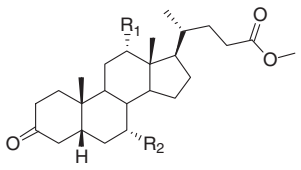
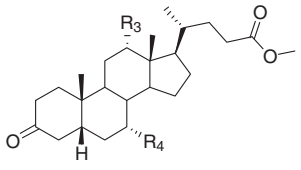
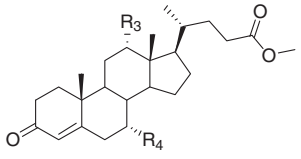
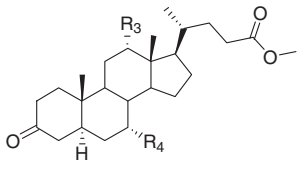
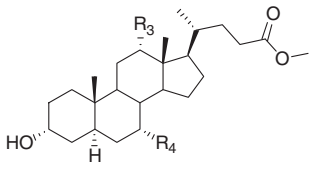
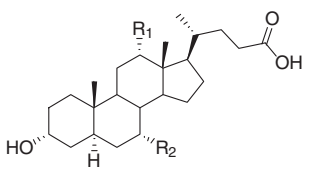
doi:10.1016/j.tetlet.2011.05.140



Scheme 1. Synthetic route to allo bile acids.

Table 1
Yields of the intermediate steps for the allo bile acids synthesis

Product		Yield (%)
	**2a**, $R_1 = R_2 = OH$	98
	2b, $R_1 = H$, $R_2 = OH$	98
	2c, $R_1 = OH$, $R_2 = H$	98
	**3a**, $R_3 = R_4 =$ MOMO	77
	3b, $R_3 = H$, $R_4 =$ MOMO	82
	3c, $R_3 =$ MOMO, $R_4 = H$	82
	**4a**, $R_3 = R_4$=MOMO	70
	4b, $R_3 = H$, $R_4 =$ MOMO	74
	4c, $R_3 =$ MOMO, $R_4 = H$	75
	**5a**, $R_3 = R_4 =$ MOMO	65
	5b, $R_3 = H$, $R_4 =$ MOMO	68
	5c, $R_3 =$ MOMO, $R_4 = H$	68
	**6a**, $R_3 = R_4 =$ MOMO	88
	6b, $R_3 = H$, $R_4 =$ MOMO	91
	6c, $R_3 =$ MOMO, $R_4 = H$	92
	**7a**, $R_1 = R_2 = OH$	92
	7b, $R_1 = H$, $R_2 = OH$	93
	7c, $R_1 = OH$, $R_2 = H$	93

study we were only interested in the 5α-reduced product. The consequence of understanding this sequential reactivity is that we do not have to saponify the C-24 ester prior to lithium–ammonia reduction as is traditionally performed.[8] It is also noteworthy that all of the other reduction methods tried, including hydride reagents and catalytic hydrogenation, selectively give 5-β reduced isomer, presumably directed by steric effects of the 7α-protected hydroxyl. Literature precedent predicted the smooth and selective reduction of the C-3 ketone to the 3α-hydroxy compound using potassium tri-*sec*-butylborohydride.[13] Removal of the protecting groups afforded the allo bile acids in very good yields over seven steps: 28–35% depending on the bile acid (see Table 1).

In summary, an efficient synthesis of 5-α reduced bile acids has been reported. This methodology not only gives the highest overall yields in shortest route reported thus far, but also provides insights into selective epimerization at ring conjunctions. Hypotheses presented on the stereoselectivity of various hydrogenation methods can serve as the guidance for reduction of enone ring junctions.

Acknowledgment

This work was supported by a National Science Foundation grant MCB-0844801 to G.P.T.

Supplementary data

Supplementary data (experimental procedures and spectrometry data of all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.140.

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