Tetrahedron Letters 52 (2011) 4512–4514

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of BCD tricyclic analogues of the novel cardiac glycoside rhodexin A

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ARTICLE INFO

Article history:
Received 3 June 2011
Revised 23 June 2011
Accepted 28 June 2011
Available online 2 July 2011

Keywords:
Diels–Alder reaction
Inverse-electron-demand
Terpene synthesis
Glycoside synthesis

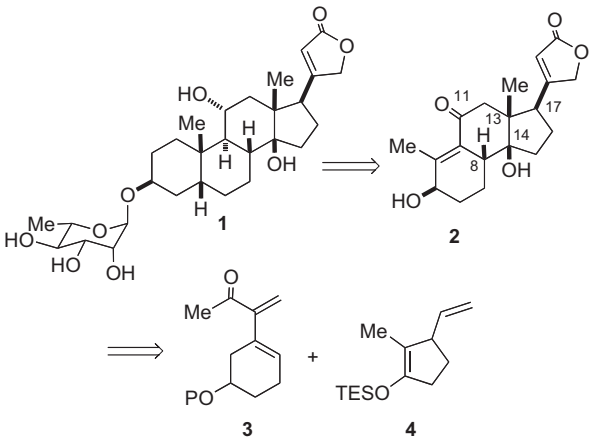
ABSTRACT

A concise synthesis of novel cardiac glycoside analogues of rhodexin A, **14** and **24**, having the BCD tricyclic system is described. The key constructive step is an inverse-electron demand Diels–Alder reaction of the silyl enol ether **4** and the 2-acetyldiene, **7** and **15**.

Cardiac glycosides are an important class of naturally occurring toxins[1] that have been used clinically for the treatment of congestive heart failure for over 200 years.[2] Named for their dramatic effect on heart, the cardiac glycosides elicit their effect by binding to myocardial Na^+,K^+ ATPase.[3] The inhibition of the Na^+ pump causes an increase in the intracellular Ca^{2+} concentration and, thus an increase of heart contraction and blood pressure.[4] This positive inotropic effect benefits the patient's weak heart by creating stronger cardiac interaction, while the increase in blood pressure is the main contributor to the toxicity of these drugs. Recently these drugs have been identified as having value in cancer therapy.[5]

Much effort toward the synthesis of new cardiac glycoside analogues has been focused on manipulation of the steroid core, as a possible method to lower the inherent toxicity of these compounds. As part of our studies toward the total synthesis of the cardiac glycosides, such as ouabain[6] and rhodexin A (**1**),[7] we have developed an efficient method[8] to synthesize the BCD system of the steroidal nucleus via an inverse-electron demand Diels–Alder reaction (Scheme 1), which would set the four desired contiguous stereocenters at C_8, C_{13}, C_{14}, and C_{17} in a single step. Thus the inverse-electron demand Diels–Alder reaction between the diene **3**, which possesses the functionality required to attach the rhamnose unit, and the dienophile **4**, the terminal alkene unit of which could be easily converted into a butenolide moiety. Here, we report the synthesis of novel cardiac glycoside analogues in which the A-ring is absent.

The synthesis of the BCD tricyclic core began with the protection of the known enynol **5**[9] as the PMB ether in 81% yield (Scheme 2). The terminal alkyne was acetylated with the acetyl Weinreb amide to give in 83% yield the enyone **6**, which was subjected to enyne metathesis conditions using Grubbs first generation catalyst to yield the desired dienone **7** in 86% yield. The vinyl silyl enol ether **4** was prepared in one step by the copper-catalyzed 1,4-addition of vinyllithium to the enone followed by trapping of the enolate in the presence of TESCl and HMPA.[10] Treating the dienone **7** and the dienophile **4** with 50 mol % of $MeAlCl_2$ at −78 °C gave the desired *exo* cycloadduct **8** in 60% yield as a 1:1 mixture of the two diastereomers at the secondary silyl ether group. Using other Lewis acids, such as $AlBr_3$/$AlMe_3$, $SnCl_4$, or triflimide (Tf_2NH), resulted in a lower yield of the cycloadduct.[8d] The



Scheme 1.

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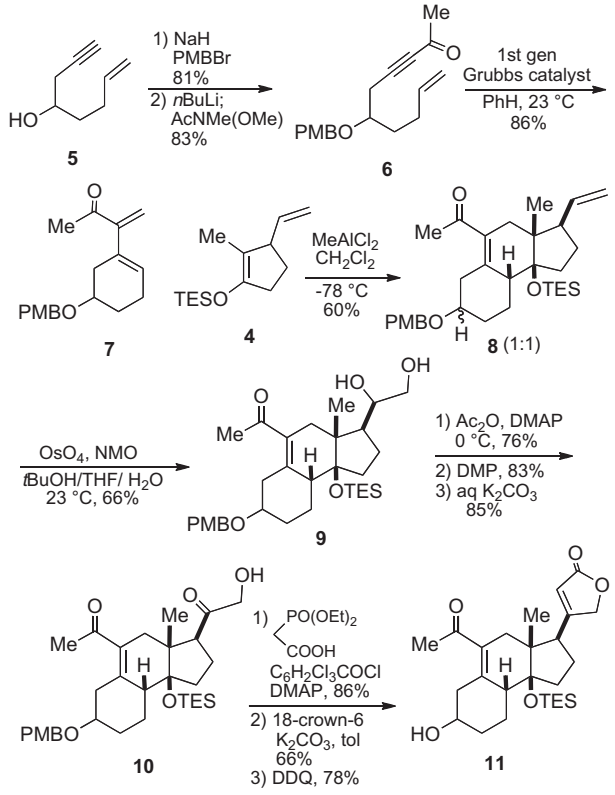
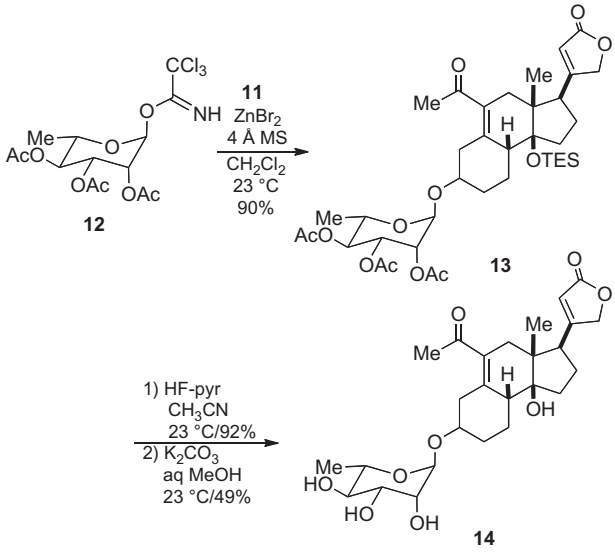
doi:10.1016/j.tetlet.2011.06.114



Scheme 2.

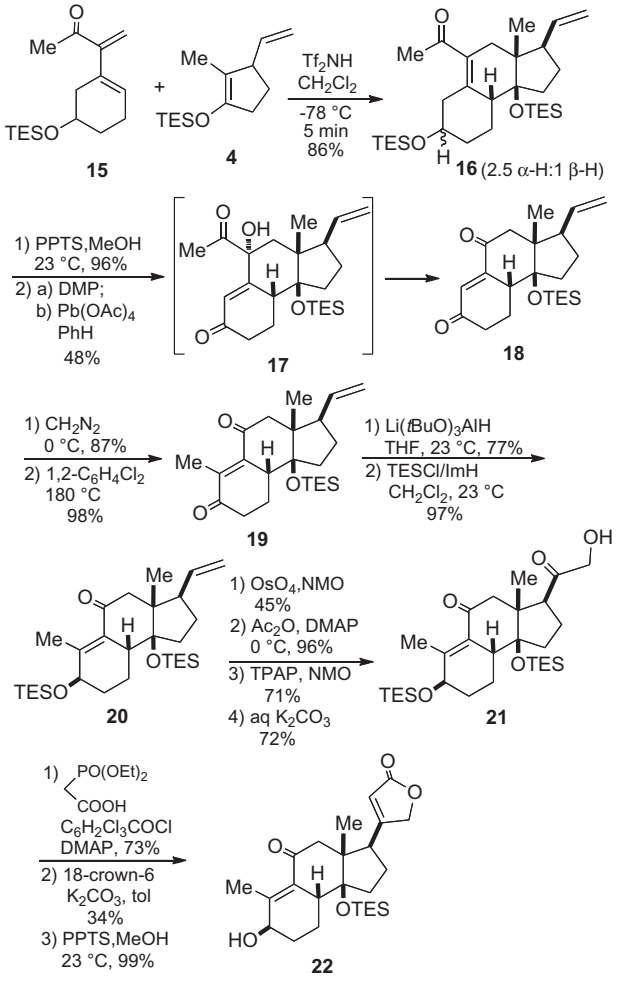
terminal double bond of the cycloadduct **8** was dihydroxylated to give the diol **9** in 66% yield. Selective protection of the primary alcohol as the monoacetate, followed by oxidation of the secondary alcohol and deprotection of the acetate group furnished the α-hydroxyketone **10** in 53% yield over three steps. The primary alcohol group in **10** was then coupled with diethylphosphonoacetic acid using Yamaguchi's reagent to furnish the phosphonate ester in 86% yield. Intramolecular Horner-Wadsworth-Emmons reaction utilizing potassium carbonate and 18-crown-6[11] yielded the desired butenolide in 66% yield. Finally, deprotection of the PMB ether with DDQ gave the desired alcohol **11** in 78% yield.



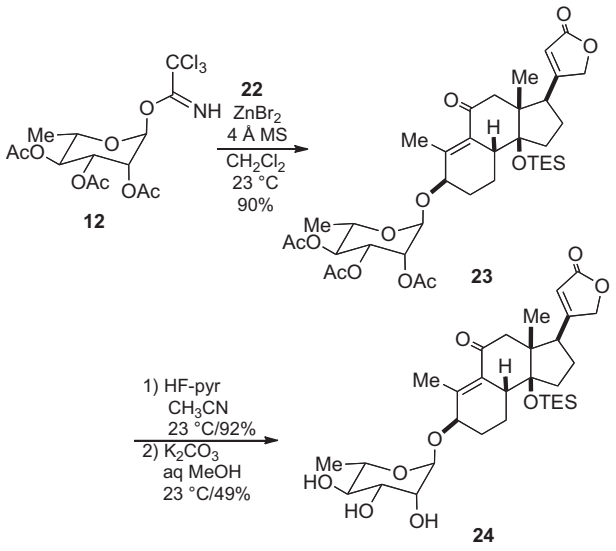
Scheme 3.

Attachment of 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl trichloroacetimidate (**12**)[12] to the tricyclic alcohol **11** was unsuccessful using TMSOTf or $BF_3{\cdot}Et_2O$ as Lewis acids. However, the use of a milder Lewis acid, such as $ZnBr_2$, gave the desired coupled product in 90% yield[13] (Scheme 3). Deprotection of the tertiary triethylsilyl ether protecting group with HF-pyridine in acetonitrile gave the tertiary alcohol in 92% yield. Final deprotection of the acetates on the sugar moiety with potassium carbonate yielded the cardiac glycoside analogue **14** in 49% yield. It should be noted that since the tricyclic system is racemic and the sugar is optically pure, there are four diastereomers formed in this process, the two alcohol stereoisomers in the B ring and the two different enantiomeric forms of the tricycle coupled to the pure sugar.

The inverse-electron demand Diels–Alder reaction was optimized by altering the protecting group on the diene and by the use of the strong Brønsted acid, triflimide (Tf_2NH).[14] Treatment of the triethylsilyl protected diene **15** (prepared from **5** by an analogous route to that described for **7**) and the dienophile **4** with 10 mol % of triflimide as the acid in dichloromethane at −78 °C for 5 min afforded the tricyclic system **16** in 86% yield as an approximate 2.5:1 mixture of the two diastereomers, with the equatorial being the major (Scheme 4). As we have shown previously, the actual catalyst is $TESNTf_2$, formed by the cleavage of a small amount of the TES silyl enol ether of **4**.[14] Mild cleavage of the less hindered silyl ether (PPTS, MeOH, 96% yield) was then followed by an unusual multi-step oxidation process using excess Dess–Martin periodinane. The secondary alcohol from **16** is oxi-



Scheme 4.



Scheme 5.

dized to the enedione which then undergoes hydroxylation (presumably via the enol) to give the α-hydroxyketone **17**. Further oxidation with DMP, or better with added lead tetraacetate, afforded the enedione **18** in 48% yield. The installation of the C_{10} methyl group was achieved through a two-step sequence involving the 1,3-dipolar cycloaddition of diazomethane to give in 87% yield the pyrazoline, followed by extrusion of nitrogen to afford the methyl enedione **19** in 98% yield.[15] Chemoselective reduction of the less hindered ketone using lithium tri(t-butoxy)aluminum hydride furnished in 77% yield the equatorial β-alcohol as a single diastereomer, which was then protected as the silyl ether **20** in 97% yield. The terminal vinyl group was then converted into the butenolide ring by the same sequence of steps described earlier. Thus osmium tetroxide-NMO dihydroxylation gave the diol, which was selectively protected to give the primary acetate. Oxidation of the secondary alcohol with TPAP/NMO[16] and deprotection of the acetate group furnished the α-hydroxyketone **21**. As before, coupling of this alcohol with diethylphosphonoacetic acid using Yamaguchi's reagent furnished the phosphonate ester and intramolecular Horner-Wadsworth-Emmons reaction gave the desired butenolide. Finally, selective deprotection of the less hindered silyl ether gave the desired alcohol **22** in 99% yield.

Attachment of 2.3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl trichloroacetimidate (**12**)[12] to the allylic alcohol **22** was again successful using the mild Lewis acid, $ZnBr_2$, to give the desired coupled product **23** in 90% yield[13] (Scheme 5). Deprotection of the tertiary triethylsilyl ether with HF-pyridine in acetonitrile gave the tertiary alcohol in 92% yield and final deprotection of the acetates provided the cardiac glycoside analogue **24** again as a mixture of two diastereomers due to the coupling of the optically pure sugar with the racemic alcohol.

In conclusion, we have successfully synthesized three novel cardiac glycoside analogues containing only the BCD tricyclic system, which was derived from a very efficient inverse-electron-demand Diels–Alder reaction. The biological activity of the analogues will be reported in due course. We also plan to utilize this synthetic strategy to prepare other cardiac glycoside analogues.

Acknowledgments

HVC gratefully acknowledges the National Institutes of Health for support via Grant No. GM08496.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.114.

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