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Enantiospecific synthesis of functionalized polyols from tartaric acid using Ley's dithiaketalization: Application to the total synthesis of achaetolide

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ABSTRACT

Synthesis of chiral tetrols and 1,2,4-triols with varied substitutions was accomplished from tartaric acid. Pivotal reaction in the synthesis was the use of Ley's dithianylation of an alkynyl ketone derived from tartaric acid. Application of the strategy was demonstrated in the total synthesis of decanolactone achaetolide.

1. Introduction

Polyols with varied substitutions are ubiquitous structural units present in a number of polyketide natural products.[1] Amongst the polyol containing compounds, the 1,2,4-triol unit **1** is a core/latent structural unit frequently encountered in a number of macrolactone natural products. Some of the examples include macrolactone natural products such as achaetolide **2**, (6*S*,7*R*,9*R*)-6,7-dihydroxy-9-propylnon-4-eno-9-lactone **3**, seimatopolide A **4**, Sch725674 **5,** and the linear polyol containing natural product fostriecin **6** (Fig. 1).

One of the best ways to synthesize the 1,3-diol present in a triol system is the reduction of the corresponding β-hydroxy ketone, which in turn can be accessed by the well-established asymmetric aldol reaction.[2] While the aldol reaction strategy renders the products with high degree of selectivity, development of non-aldol reaction for aldol products is of significant importance in organic synthesis. In this context, pioneering work by Smith's group established the use of 1,3-dithiane linchpins as excellent acyl anion equivalents and has exemplified their use in the synthesis of structurally complex natural products.[3] An attractive strategy for the synthesis of β-ketodithianes, a virtual surrogate of 1,3-diols is the procedure reported by Ley's group utilized the addition of 1,3-propanedithiol to alkynyl ketones.[4] Generality of this reaction is showcased by Ley's group by the synthesis of an impressive array of compounds. Herein, we report a facile approach for polyol synthesis, particularly to the synthesis of 1,2,4-triols utilizing a combination of chiral pool tartaric acid and Ley's dithiaketalization reaction and application of the strategy to the total synthesis of decanolactone natural product achaetolide.

2. Results and discussion

For a decade, our efforts in the use of chiral pool tartaric acid in natural product synthesis culminated in establishing the γ-hydroxy amides derived from tartaric acid as excellent building blocks.[5] Key reaction in our methodology is the desymmetrization of tartaric acid amide **7** with various alkyl/aryl and alkenyl Grignard reagents followed by stereoselective reduction of the resultant ketones. We reasoned that the addition of alkynyl Grignard reagents would lead to the mono keto amide **8**, which on Ley's dithiaketalization should provide the β-1,3-dithianyl ketone **9**. Elaboration of **9** will lead to the polyol systems **10, 11** or **12** present in a number of natural products (Scheme 1).[6]

Accordingly, the synthetic sequence commenced with the

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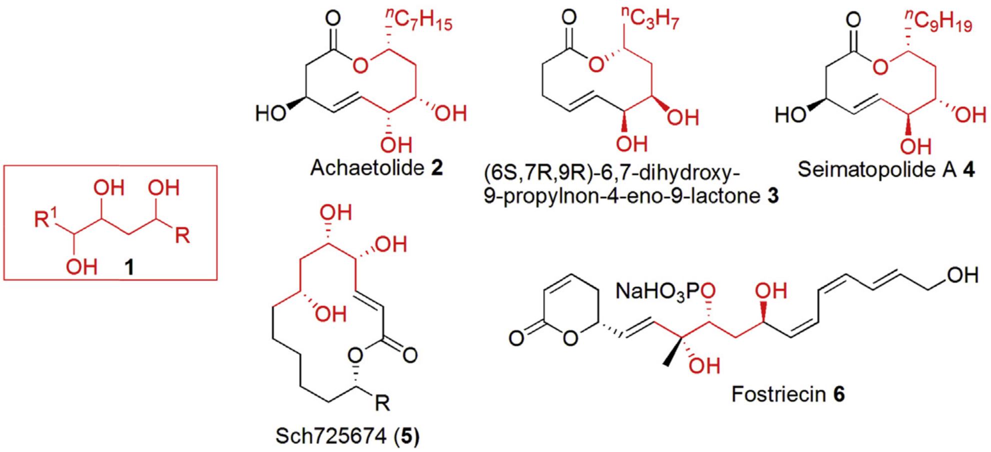
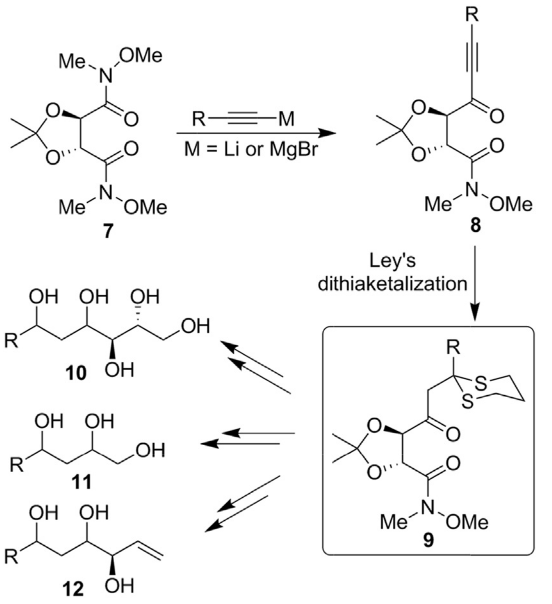


Fig. 1. Natural products possessing the 1,2,4-triol unit.



Scheme 1. Proposed synthesis of polyols from the bis-Weinreb amide of tartaric acid.

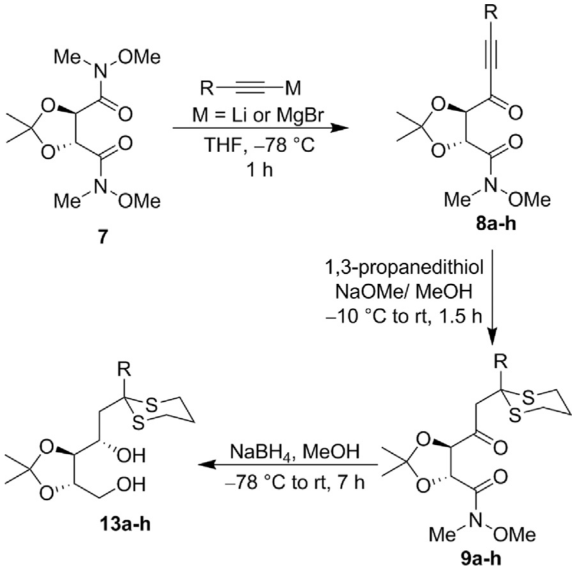
Table 1
Synthesis of alkynyl ketones **8a-h** from the *bis*-Weinreb amide **7** and their elaboration to polyhydroxy 1,3-dithiane **13a-h.**

S. No.	R–C≡C–M	Yield %[a]		
		8	9	13
1	H–C≡C–MgBr	**8a** (48)[b]	**9a** (84)	**13a** (75)
2	H_3C–C≡C–MgBr	**8b** (65)	**9b** (88)	**13b** (81)
3	CH_2=CH–$(CH_2)_2$–C≡C–MgCl	**8i** (63)	**9i** (97)	**13i** (95)
4	Me_3Si–C≡C–Li	**8c**-[c]	**9c** (64)[d,e]	**13a** (75)[f]
5	Ph-C≡C–Li	**8d** (60)	**9d** (90)	**13d** (71)
6	H_7C_3–C≡C–Li	**8e** (88)	**9e** (98)	**13e** (82)
7	$H_{13}C_6$–C≡C–Li	**8f** (63)	**9f** (95)	**13f** (85)
8	$H_{15}C_7$–C≡C–Li	**8g** (89)	**9g** (96)	**13g** (82)
9	TBSO–$(CH_2)_3$–C≡C–Li	**8h** (76)	**9h** (95)	**13h** (87)

[a] All yields refer to yields after chromatography.
[b] Formation of the enamine **8aa** (29% yield) resulting from the addition of *N,O*-dimethoxy hydroxylamine (Weinreb amine) to the alkynone **8a** is observed. See ref. [9] and supporting information.
[c] Monoalkyl ketone **8c** is not isolated and is proceeded to the next step without purification.
[d] Yield obtained after two steps.
[e] 24% of the desilyalted product **9a** was also obtained.
[f] Reduction always led to the formation of desilylated product **13a**.

addition of R–C≡C–Li/MgBr to the *bis*-Weinreb amide **7**[7] derived from tartaric acid to afford the mono-keto amides **8a-h** in 48–89% yield. Addition of 1,3-propanedithiol to the alkynyl ketones **8a-h** under Ley's conditions (NaOMe/MeOH) was facile and the corresponding β-dithianyl ketones **9a-h** were obtained in excellent yields (see Table 1). Stereoselective reduction of **9a-h** with excess $NaBH_4$ afforded the corresponding 1,4-diol **13a-h** in good yields as a single diastereomer (*erythro* isomer) (Scheme 2).[8] It is worth noting that the reduction of structurally similar γ-oxoamides devoid of the dithiane moiety with K-Selectride furnished the corresponding *threo* isomer.[6a,8b] This observation has been used for the assignment of stereochemistry at the newly formed stereo center in **13a-h**.

Thus, desulfurization of the 1,3-dithiane moiety in **13g** furnished the 1,4-diol **14** possessing the *erythro* stereochemistry. Comparison of the physical and spectral properties of **14** with the corresponding known *threo* isomer **16** obtained by from the γ-oxo-amide **15** (see Supporting Information for the synthesis of **16**) provided an indirect proof for the formation of the *erythro* isomer at the newly formed stereocenter in **13g** (Scheme 3). The stereochemistry at the



Scheme 2. Synthesis of polyhydroxy 1,3-dithiane from tartaric acid amide.