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Synthesis and Determination of Absolute Configuration of a Divergent Polyhydroxy Enyne Compound

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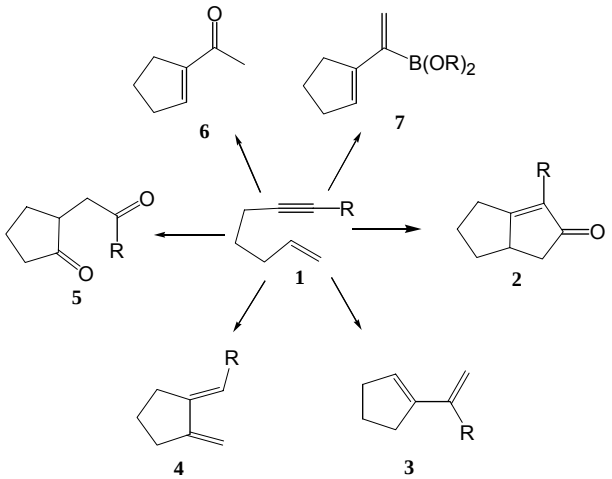
Abstract: Polyhydroxy enyne compound (+)-(1′S, 2R, 3S, 5S, 6S)-5,6-dimethoxy-5, 6-dimethyl-2-(1'-hydroxylpropyl-2-ne)-3-vinyl-1,4-dioxane has been synthesized from D-(-)-tartaric acid. A new chiral center was established by nucleophilic addition with 87% de. The modified Mosher's method was employed to confirm the absolute configuration of **17**, which assigned the S-configuration at the new chiral center.

Keywords: Tartaric acid, enyne compound, nucleophilic addition, modified Mosher's method.

Enyne compound is a divergent intermediate that can be converted to a series of fused ring systems as well as monocyclic compounds (**Scheme 1**).

Enyne, especially chiral enyne compound, is a useful building block for the synthesis of natural products, such as pentalenic acid[1], dendrobine[2], and iridomyrmecin[3]. Herein, we report the stereoselective synthesis of a polyhydroxy enyne intermediate, and the determination of its absolute configuration.

Scheme 1



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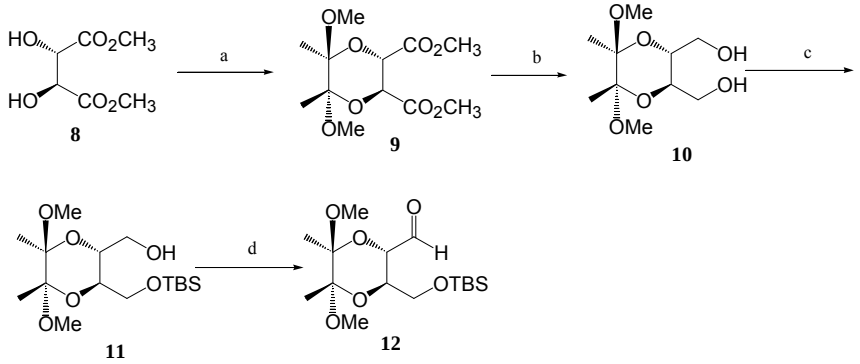
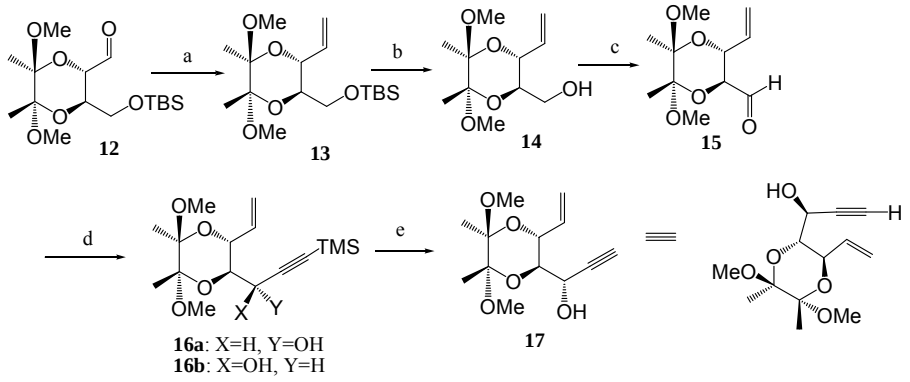
Scheme 2 The synthesis of aldehyde **12**



Reagents and conditions: a) butane-2,3-dione, CSA, $CH(OCH_3)_3$, CH_3OH, reflux, 14 h 70%; b): $LiAlH_4$, THF, reflux, 3 h, 85%; c): NaH, TBSCl, THF, rt, 3 h, 90%; d): $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78°C.

Scheme 3 The synthesis of chiral polyhydroxy enyne compound **17**



Reagents and conditions: a): NaH, DMSO, Ph_3PCH_3I, rt, 2 h, 86% (two steps); b): TBAF, HOAc, THF, 50°C, 3 h, 100%; c): $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78°C. d): trimethylsilylacetylene, Mg, EtBr, THF, -78°C, 1 h, 65%(two steps), 87% de.; e) TBAF, THF, rt, 0.5-1 h, 100%.

The synthesis of chiral polyhydroxy enyne compound **17** was started from the aldehyde **12** which was prepared from D-(-)-tartaric acid according to the ptotocol reported by Steven V. Ley[4](**Scheme 2**).

With **12** in hand, we focused on the synthesis of compound **17**(**Scheme 3**). According to the report by Abad[5], we used $NaCH_2SOCH_3$, prepared from sodium hydride and DMSO, as the base which reacted with methyl triphenylphosphonium iodide to form ylide, then reaction of **12** with the Wittig reagent at room temperature for 2 h, we obtained compound **13** as colorless oil in 86% yield. Then treatment of **13** with TBAF (5 equiv) and glacial acetic acid (5 equiv) in THF at 50°C for 3 h, we successfully synthesized **14** as colorless oil in quantitation[6]. Absence of glacial acetic acid will prolong the reaction time and make the purification difficult. Standard Swern oxidation[7] of the residual alcohol **14** to the aldehyde **15** occurred smoothly and in good yield. **15** was stable for several days at room temperature and could be used directly to

the next reaction without further purification. Diastereoselective nucleophilic addition to aldehyde **15** in THF at -78°C with trimethylsilylacetylide magnesium bromide[8], which was freshly prepared by addition of trimethylsilylacetylide to ethyl magnesium bromide in anhydrous THF, we obtained the diastereoisomeric mixture of **16a** and **16b**. The diastereoisomeric products were easily separated by silica gel chromatography, and the yield of the product **16a** was 70%, **16b** was 4.6%. Thus the reaction diastereoselectivity was 87% de. Increasing the temperature of the reaction will result in increasing the yield of **16b**. Then desilylation[9] of **16a** with TBAF (0.6 equiv) in THF at room temperature for 0.5 h we synthesized the target compound **17**[10] as white solid with 30% of total yield from D-(-)-tartaric acid.

A modified Mosher's method was employed to elucidate the absolute configuration of the new chiral center in **17**. Compound **17** was treated with (R)-(+)- and (S)-(-)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA) in the presence of DCC and DMAP at room temperature for 4 h to afford (R)-(+)- and and (S)-(-)-MTPA esters[11], then the ^{1}H-NMR spectroscopy was detected.

Kakisawa and coworkers[12] had established a model to elucidate the absolute configuration of secondary alcohols with use of high-field FT NMR Spectroscopy (**Figure 1 Model B**). According to their report, the value of the chemical shift differences between the (R)- and the (S)-MTPA esters [$\Delta\delta = \delta_s - \delta_R$] were calculated (**Figure 1 Model A**), and then put the protons with positive Δδ on the right side and those with negative Δδ on the left side of the model B. So the compound **17** was assigned S- configuration at the new chiral center.

Figure 1 Models to elucidate the absolute configuration

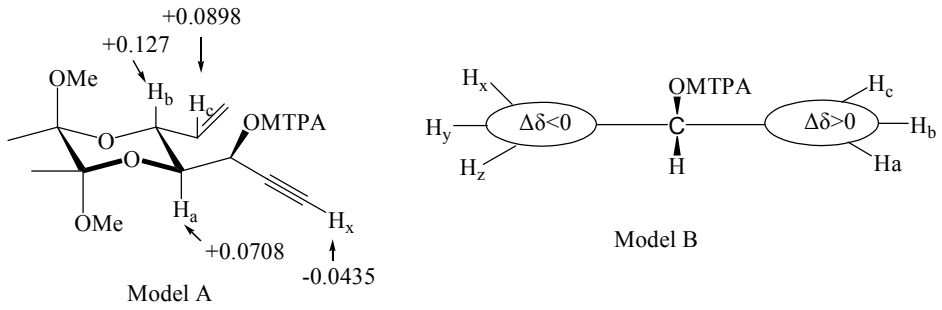


Figure 2 ROSEY of tetraacetyl 4a-carbaxylose

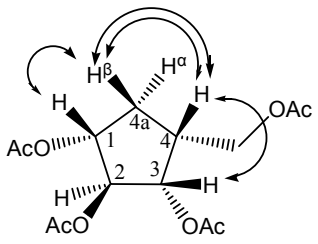


Table 1 ^{1}H NMR and ROSEY spectral data for tetraacetyl 4a-carbaxylose in $CDCl_3$

Position	1	2	3	4	4aα	4aβ
^{1}H NMR	5.04, m, 1H	5.14, m,	5.12, m,	2.62, m, 1H	1.68, m, 1H	2.41, m, 1H
ROSEY	H-4aβ, H-3, H-4	1H, H-4aα	1H, H-1, H-4	H-4aβ, H-1, H-3	H-4aβ, H-2	H-4aα, H-1, H-4

The configuration of **17** was further proved by ROSEY spectroscopy when we synthesized one of our terminal compounds tetracetal 4a-carbaxylose from compound **17** (**Figure 2**). H-3, H-1, H-4aβ and H-4 have correlations in ROSEY spectroscopy (**Table 1**). We have known that C-1 is R-configuration which origins in D-(-)-tartaric acid, so we can assign S-configuration at C-3.

In conclusion, we prepared chiral polyhydroxy enyne compound with good stereoselectivity, which involved nine steps starting from commercially available, inexpensive tartaric acid with 30% of total yield. The synthetic sequence described provides an access to the chiral polyhydroxy enyne compound of potential value in the synthesis of natural products.

References and Notes

1. G. Agnel, E. Negishi, *J. Am. Chem. Soc.*, **1991**, *113*(19), 7424.
2. M. Mori, N. Uesaka, M. Shibasaki, *J. Org. Chem.*, **1992**, *57*(13), 3519.
3. G. Agnel, Z. Owezarkzyk, E. Negishi, *Tetrahedron Lett.*, **1992,** *33*(12), 1543.
4. J. S. Barlow, D. J. Dixon, S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, **1999**, *12*, 1627.
5. A. Abad, C. Agullō, A. C. Cuńat, R. H. Perní, *J. Org. Chem.*, **1999**, *64*(5), 1741.
6. L. Davidson, A. Blencowe, M.G. Drew, W. Hayes, *J. Mater. Chem*., **2003**, *13*(4), 758.
7. K. Omura, D. Swern, *Tetrahedron*, **1978**, *34*(11), 1651.
8. A. Mauvais, C. Hetru, B. Luu. *Tetrahedron Lett.*, **1993**, *34*(27), 4337.
9. T. Nishikawa, A. Ino M. Isobe, *Tetrahedron*, **1994**, *50*(5), 1449.
10. Date of compound **17**: mp 74-76℃; $[\alpha]_D^{20}$: +198.7 (c 1.70 $CHCl_3$); IR (KBr, cm^{-1}): 3296 and 2121(CCH), 1641($CHCH_2$); ESI-MS: *m/z* 279 (M^++ Na); ^{1}H NMR ($CDCl_3$, 400MHz, δ ppm): 1.30(s, 3H), 1.34(s, 3H), 2.41(d, 1H, J=2.29Hz), 3.25(s, 3H), 3.31(s, 3H), 3.67(dd, 1H, J=9.93, 1.68Hz), 4.30(dd, 1H, J=9.93,7.94Hz), 4.36(t, 1H, J=1.68Hz), 5.44(m, 2H), 5.82(m, 1H); ^{13}C NMR($CDCl_3$,400MHz): 17.6, 17.8, 48.0(2C), 61.1, 70.1, 72.6, 73.2, 82.7, 98.5, 99.2, 120.9, 133.2; Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92, H, 7.86; Found: C, 60.95, H, 7.80.
11. T. Sunazuka, M. Handa, K. Nagai, *et al.*, *Tetrahedron*, **2004**, *60*(36), 7845.
12. I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.*, **1991**, *107*(15), 4586.

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