Tetrahedron Letters 54 (2013) 7059–7061

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Early introduction of the amino group to the C27–C35 building block of Eribulin

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ARTICLE INFO

Article history:
Received 21 August 2013
Revised 11 October 2013
Accepted 16 October 2013
Available online 22 October 2013

Keywords:
Eribulin
Halichondrin B
Ammonolysis
1,2-Amino alcohols

ABSTRACT

A new synthetic strategy towards the C27–C35 subunit of Eribulin (**1**) has been devised to include a protected 1,2-amino alcohol at C34–C35. Early introduction of the C35 amino group in the synthesis of **1** increases the efficiency of the route. This new approach can be accomplished on a multi-gram scale and allows for the successful synthesis of Eribulin.

Introduction

Eribulin (**1**), is a fully synthetic analog of the marine natural product Halichondrin B (**2**), a congener of the Halichondrin polycyclic macrolides first isolated from the marine sponge *Halichondria okadai* by Uemura, Hirata and co-workers (Fig. 1).[1–3] This class of molecules initially received much attention due to their structural complexity, in addition to their in vitro and in vivo anti-tumour activity.[3] Following the first total synthesis of **2** by Kishi and co-workers,[2a] extensive drug discovery efforts were undertaken resulting in the discovery of Eribulin that has been recently approved by the FDA as a mesylate salt for the treatment of certain patients with metastatic breast cancer.[4]

The synthesis of **1** represents a formidable challenge, particularly when considering a scale-up development for industrial manufacture of this substance as an active pharmaceutical ingredient. The most common synthetic strategy relies on the convergent assembly of subunits **3**–**5**, followed by macrocyclization, formation of the polycyclic ketal moiety and completed by the introduction of the primary amine at C35 (Scheme 1).[5]

From a standpoint of synthetic scale-up development, we envisioned that establishment of the amino functionality at C35 much earlier in the synthesis of **1** would greatly improve the efficiency of the route. In particular, the conversion of **7** into **1** (Scheme 2) requires tosylation of the primary alcohol, which upon treatment with alcoholic ammonium hydroxide, forms epoxide **9**. Intermediate **9** reacts further with ammonia to provide **1**. Utilizing this strategy at the end of the synthesis can be particularly problematic, as the primary amine that is formed in **1** is more reactive than ammonia and may react with **9** instead, thereby generating dimeric byproduct **10**.[6] Early introduction of the C35 amino group would avoid this byproduct formation and loss of precious material at the end of the multistep synthetic sequence. In general, fewer synthetic steps would be necessary at the later stages of production, which would involve more costly and potentially cytotoxic intermediates, including difficult handling in isolation suites. Furthermore, we hoped that early introduction of an amine would provide an opportunity for crystalline intermediates via ammonium salts, to assist in their purification. Thus, we looked towards the construction of the C27–C35 subunit as a convenient point to introduce the C35 amino group, with our results presented herein (See Scheme 3).

Results and discussion

Beginning from advanced intermediate **11**,[7] the secondary alcohol is oxidized to ketone **12** via Swern oxidation and subsequently undergoes a Horner–Wadsworth–Emmons reaction to afford unsaturated aryl sulfones **14a** and **14b**, as a mixture of *Z*:*E* geometrical isomers. We found the *Z*:*E* selectivity of the Horner–Wadsworth–Emmons reaction to be highly dependent on the nature of the *O*-alkyl group of the phosphonate coupling partner (**13**, Table 1).[8] The ratio of *Z*:*E* increases significantly as the steric bulk of R increases from Me to *i*-Pr (entries 1–3). High ratios of the *Z* geometrical isomer proved to be integral in later stages of the synthetic route (vide infra).

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http://dx.doi.org/10.1016/j.tetlet.2013.10.077

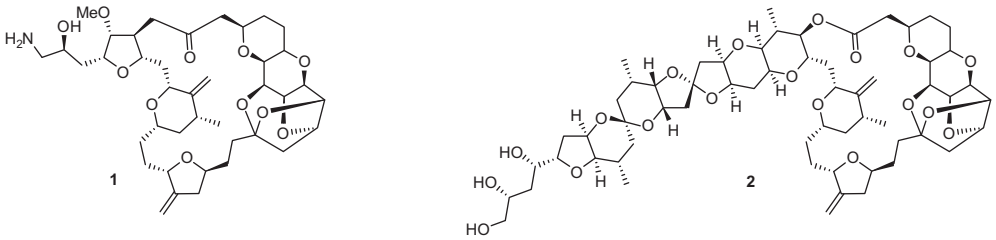
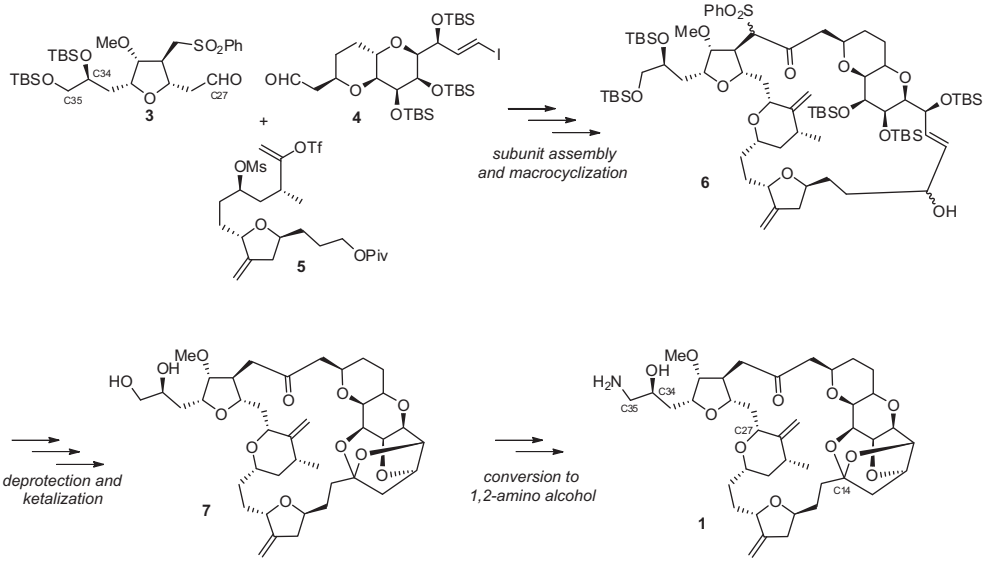
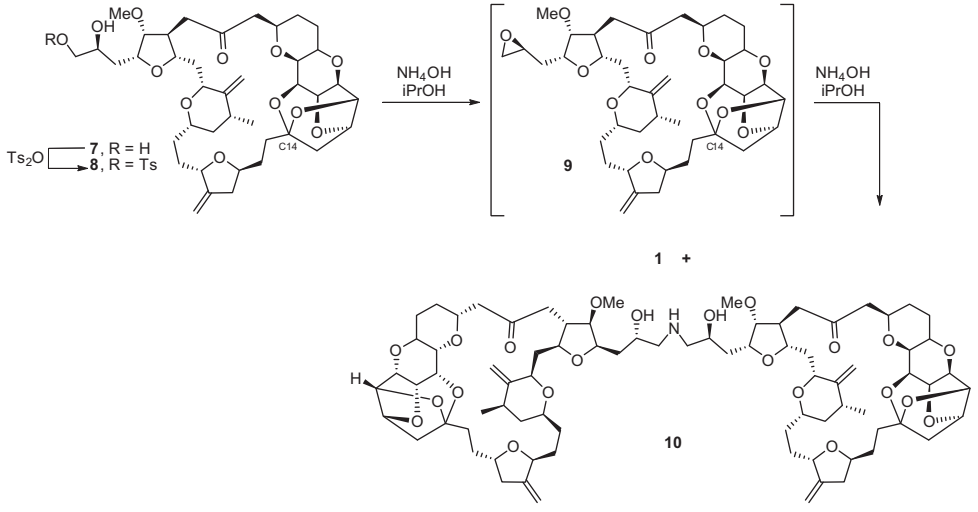


Figure 1. Structures of Eribulin (**1**) and Halichondrin B (**2**).

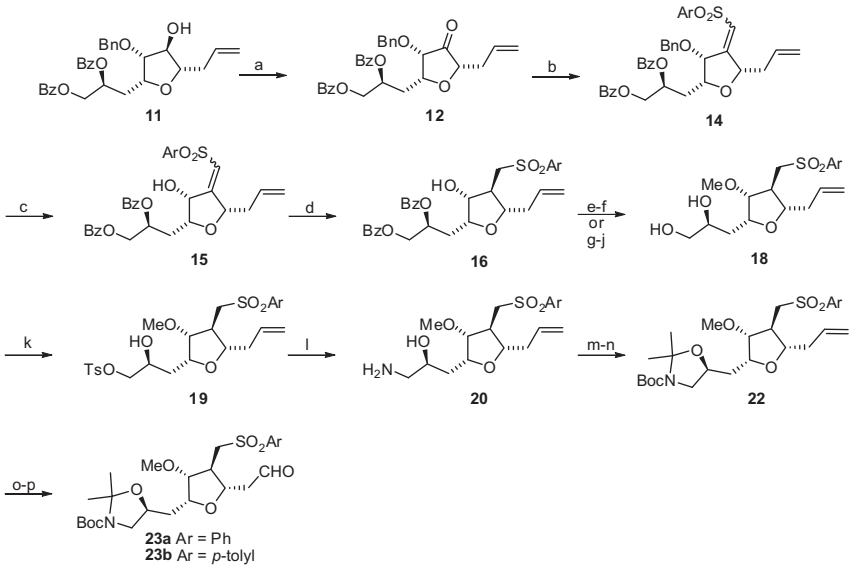


Scheme 1. Synthetic route to Eribulin.



Scheme 2. Late stage amination of C35 to form **1** and potential byproduct **10**.

The benzyl group was removed according to known procedures to give secondary alcohol **15**, which subsequently directs the selective reduction of the vinyl sulfone to afford **16**. In our hands, the minor *E* geometrical isomer of **14** reacted significantly slower, or not at all, in the removal of the benzyl group and the selective reduction of the vinyl sulfone, thus necessitating the high levels of *Z* selectivity in the synthesis of **14**. Diol **18** can be accessed by the selective methylation of the secondary alcohol with trimethyloxonium tetrafluoroborate and proton sponge,[9] followed by the basic methanolysis of the benzoyl groups. Alternatively, **18** can be furnished by basic methanolysis of the benzoyl groups to yield a triol, selective protection of the 1,2-diol as the acetonide, methylation of the free secondary alcohol with MeI and removal of the acetonide. The primary alcohol is converted to tosylate **19**, which then undergoes a three-step sequence of ammonolysis,[6] Boc- and acetonide[10] protection to afford the protected 1,2-amino alcohol **22**. The sequence is completed by dihydroxylation of the terminal olefin, followed by periodate cleavage to afford aldehyde **23**. This sequence



Scheme 3. Synthetic route towards C27–C35 building block 23. *Reagents and conditions:* (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (b) $(RO)_2P(O)CH_2SO_2Ar$ (**13a–d**), LHMDS, toluene, 85–100% over 2 steps; (c) TMSI, CH_3CN, 73%; (d) $NaBH(OAc)_3$, Bu_4NCl, toluene/DME, 78%; (e) Me_3OBF_4, proton sponge, CH_2Cl_2, 83%; (f) K_2CO_3, MeOH, quant; (g) K_2CO_3, MeOH; (h) 2,2-dimethoxypropane, pTSA-H_2O, acetone; (i) MeI, KO^{t}Bu, THF; (j) 2 N HCl, MeOH 87% over 4 steps; (k) TsCl, Et_3N, Bu_2SnO, CH_2Cl_2, 80–85%; (l) 7 N NH_3/MeOH; (m) Boc_2O, NaOH, dioxane 80–87% over 2 steps; (n) 2,2-dimethoxypropane, pTSA-H_2O, acetone 79–85%; (o) OsO_4, NMO, CH_2Cl_2; (p) $NaIO_4$, EtOAc/H_2O, 77–83% over 2 steps.

Table 1
Dependence on the structure of phosphonate **13** ($(RO)_2P(O)CH_2SO_2Ar$) towards the *Z*:*E* selectivity in the Horner–Wadsworth–Emmons reaction

Entry	Phosphonate	R	Ar	Product	*Z*:*E* (**14**)[a]
1	**13a**	Me	Phenyl	**14a**	5:1
2	**13b**	Et	Phenyl	**14a**	8:1
3	**13c**	*i*-Pr	Phenyl	**14a**	27:1
4	**13d**	Et	*p*-Tolyl	**14b**	6:1

[a] *Z*:*E* ratio determined by ^{1}H NMR.

can be conveniently carried out on >100 g scale to afford multi-gram quantities of **23**. Compound **23** has been applied in the successful synthesis and isolation of Eribulin, moreover with fewer transformations after the installation of the polycyclic ketal moiety at C14 and without formation of the undesired dimer **10**.

In conclusion, we have demonstrated that the C35 amino group of Eribulin (**1**) can be easily introduced during the construction of the C27–C35 subunit **23** and carried forward as a protected 1,2-amino alcohol. This sequence is amenable to an industrial scale and will aid at increasing the overall efficiency of the commercial synthesis of **1**.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.077.

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