RSC Advances

RSC Publishing

COMMUNICATION

View Article Online
View Journal

Practical synthesis of fingolimod from diethyl acetamidomalonate†‡

Cite this: DOI: 10.1039/c3ra40894a

Received 21st February 2013,
Accepted 3rd May 2013

DOI: 10.1039/c3ra40894a

www.rsc.org/advances

Bhaskar Kandagatla,[a] Vetukuri Venkata Naga Kali Vara Prasada Raju,[b] Narayana Sravan Kumar,[a] Ganta Madhusudhan Reddy,[b] Katkam Srinivas,[b] Javed Iqbal,[a] Rakeshwar Bandichhor[b] and Srinivas Oruganti*[a]

A facile six-step synthesis of fingolimod, starting from readily available and inexpensive starting material diethyl acetamidomalonate, in very good yield is demonstrated.

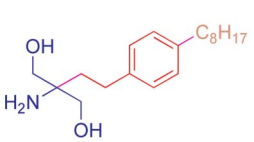
Fingolimod (FTY720, Gilenya) **1** is a classic example of a drug which is inspired by a natural product, in this case myriocin (ISP-1), a metabolite of the fungus *Isaria sinclairii* (Fig. 1).[1] The USFDA has approved Gilenya (fingolimod) for oral treatment of Multiple Sclerosis (MS) recently. It is a structural analogue of sphingosine that is phosphorylated by sphingosine kinases in cells.[2–4] Fingolimod **1** acts as a nonselective agonist of the sphingosine-1 phosphate receptor expressed by lymphocytes, and prevents lymphocyte emersion from secondary lymphatic organs and their subsequent movement into sites of inflammation.[5] Fingolimod **1** has emerged as a promising oral drug for MS with a significant reduction in relapses observed in patients treated with the drug.[6]

The key challenge in the synthesis of fingolimod [2-amino-2-(4-octylphenethyl)propane-1,3-diol] **1** is the construction of the hydrophilic 2-aminopropane-1,3-diol head group and most of the literature routes have focused on approaches for the construction of the same. An early synthesis of fingolimod **1** by Adachi and co workers employed alkylation of diethyl 2-acetamidomalonate with 1-(2-bromoethyl)-4-octylbenzene to obtain the Adachi–Fujita intermediate diethyl 2-acetamido-2-(4-octylphenethyl)malonate which was then delineated to fingolimod **1**.[7] The other literature syntheses of **1** start from building blocks such as 4-octylbenzaldehyde or 2-(4-octylphenyl)ethanol, which were conjugated to the polar head-group derived from diethyl acetamidomalonate,[8] TRIS-derivatives[9] or from a bis-aldol addition with 2-aryl substituted ethyl nitrate.[10] One of the problems with the late stage introduction of the polar head group is the increased presence of impurities related to the chemistry involved in the introduction of the *N*-acetamido-1,3-propanediol moiety. We therefore decided to install the polar head group first and then exploit its presence for the synthesis of fingolimod **1** hydrochloride in an efficient and cost-effective manner (Fig. 2).

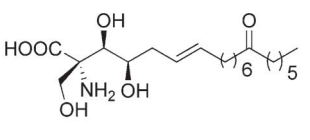
As a part of our ongoing program on scalable and cost-effective routes for active pharmaceutical ingredients, we were interested in the synthesis of fingolimod **1** since it is a promising oral drug for multiple sclerosis. Some of the literature routes had the disadvantage of including complicated steps which lead to intermediates as oily substances or various isomeric mixtures. Consequently, isolation and purification of the intermediate products by conventional methods such as chromatography rendered the processes unviable for the large-scale preparation of **1**.

Herein, we report a six step synthesis of fingolimod **1** (Scheme 1) starting from the readily available starting material diethyl acetamidomalonate **2**. Unlike hitherto known routes, which involved the insertion of the head group at the end, we decided to start the synthesis from the head group. The first step involved the alkylation of **2** with phenethylbromide. Due to the competing nucleophilic substitution *vs.* elimination during alkylation reactions with **2**, we decided to focus on improving the alkylation step. An initial screening of a selection of appropriate bases, solvents and temperatures revealed that bromide elimination to the styrene was the predominant by-product under most conditions (Table 1).

Nucleophilic substitution of phenethylbromide with consistent yields and reproducibility was achieved using cesium carbonate as



Fingolimod 1



Myriocin (thermozymocidin- ISP-1)

Fig. 1 Structures of fingolimod **1** and myriocin.

[a]*Center for Process Research & Innovation, Dr Reddy's Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad 500 046, India. E-mail: soruganti@drils.org*

[b]*API R&D, IPDO-Innovation Plaza, Dr Reddy's Laboratories Ltd, Bachupally, Qutubullapur, Hyderabad 500 072, India*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra40894a

‡ Dedicated to Dr Kallam Anji Reddy (1940–2013); DRL-IPD Communication No.: IPDO-IPM-00358.

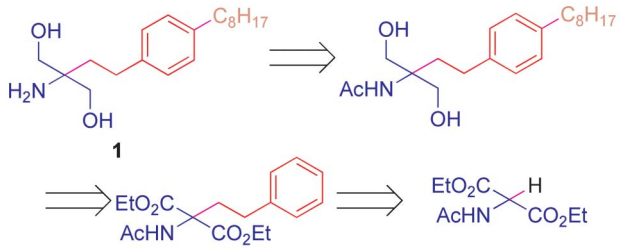


Fig. 2 A retrosynthetic approach to fingolimod **1**.

the base and DMSO as the solvent. Under these conditions, we were able to prepare **3** conveniently in a 75% yield, without the formation of styrene or impurities derived from partial deacetylation.

Reduction of the ethyl esters of compound **3** was carried out using sodium borohydride in methanol to obtain diol **4** in very good yield and with high purity. During our initial screening, we employed LAH for the reduction. However, sodium borohydride was milder and easier to handle and a scalable process on a 200 g scale was established wherein the purification could be carried out without column chromatography. The diol **4** was acetylated using acetic anhydride in the presence of pyridine to furnish the diacetate **5**.

Subsequently, the diacetate **5** was taken up for Friedel–Crafts acylation with octanoyl chloride to obtain the desired *para*-acylated product **6** exclusively in good yield. This process was further optimized on a multigram scale and the purification of the product was carried out without resorting to column chromatography. The *N*-acetamido diester head group presumably imparted the desired steric influence to reduce the formation of the *ortho*-acylated product during the Friedel–Crafts acylation. Similar results were observed when $SnCl_4$ or $TiCl_4$ were employed for the reaction, but the yields were marginally lower compared to the reaction mediated by $AlCl_3$.

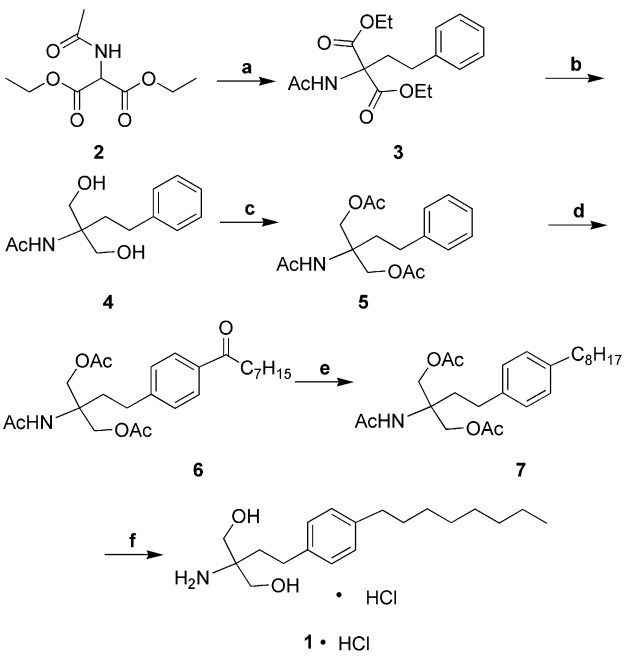
Reduction of the ketone in compound **6** to a methylene group was carried out by hydrogenation with 10% Pd/C in EtOH, to afford **7** in quantitative yields. A one pot hydrolysis of acetamide and diacetates was carried out by employing 6 N aq. HCl under reflux conditions to give fingolimod **1** as the hydrochloride salt in good yield. Further re-crystallization using ethanol afforded the hydrochloride salt of **1** with purity greater than 99%.

In conclusion, a safe, reproducible, high-yielding, and robust route for the synthesis of fingolimod **1** starting from diethyl acetamidomalonate is reported.[11] The present work demonstrates that initial installation of the polar 2-amino-1,3-propanediol head group can significantly reduce the impurities associated with the polar head group in the final steps. Avoidance of hazardous reagents, expensive catalysts, isomeric mixtures and difficult purification methods renders this route a cost-effective process for fingolimod **1**, which can be translated into an industrially viable process.

Table 1 Screening of bases for the alkylation of **2** with phenethyl bromide

Entry	Base	Solvent/Temp./Time	Yield
1	KH_2PO_4	DMSO/60 °C/6 h	30%[a]
2	NaH	DMF/RT/16 h	10%[a,b]
3	NaH	DMA/70 °C/4 h	10%[a,b]
4	NaOEt	EtOH/65 °C/4 h	30%[a]
5	NaOEt[c]	EtOH/65 °C/4 h	55%
6	NaOEt	THF/50 °C/6 h	15%[a]
7	Cs_2CO_3	DMF/60 °C/7 h	55%
8	Cs_2CO_3	DMSO/65 °C/6 h	75%

[a] Styrene was the major product. [b] A mixture of products was obtained which included partially deacetylated products. [c] In the presence of KI.



Scheme 1 *Reagents and conditions*: (a) Phenethylbromide, Cs_2CO_3, DMSO, 65 °C, 6 h, 75%; (b) $NaBH_4$, MeOH, 0 °C–RT, 18 h, 88%; (c) Ac_2O, Pyridine, RT, 15 h, 90%; (d) Octanoyl chloride, $AlCl_3$, EDC, 0 °C–RT, 18.5 h, 81%; (e) 10% Pd–C, EtOH, H_2, RT, 2 h, 95%; (f) 6 N aq. HCl, 100 °C, 1 h, 79%.

Acknowledgements

We thank Dr Reddy's Institute of Life Sciences and Dr Reddy's Laboratories Ltd. for supporting this work.

Notes and references

1 T. Fujita, K. Inoue, S. Yamamoto, T. Ikumoto, S. Sasaki, R. Toyama, K. Chiba, Y. Hoshino and T. Okumoto, *J. Antibiot.*, 1994, **47**, 208.
2 S. W. Paugh, S. G. Payne, S. E. Barbour, S. Milstien and S. Spiegel, *FEBS Lett.*, 2003, **554**, 189.
3 A. Billich, F. Bornancin, P. Dévay, D. Mechtcheriakova, N. Urtz and T. Baumruker, *J. Biol. Chem.*, 2003, **278**, 47408.
4 T. Sanchez, T. Estrada-Hernandez, J. H. Paik, M. T. Wu, K. Venkataraman, V. Brinkmann, K. Claffey and T. Hla, *J. Biol. Chem.*, 2003, **278**, 47281.

5 (*a*) L. Kappos, J. Antel and G. Comi, *N. Engl. J. Med.*, 2006, **355**, 1124; (*b*) V. Brinkmann, *Br. J. Pharmacol.*, 2009, **158**, 1173.
6 N. Mulakayala, P. Rao, J. Iqbal, R. Bandichhor and S. Oruganti, *Eur. J. Med. Chem.*, 2013, **60**, 170.
7 K. Adachi, T. Kohara, N. Nakao, M. Arita, K. Chiba, T. Mishina, S. Sasaki and T. Fujita, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 853.
8 S. Sugiyama, S. Arai, M. Kiriyama and K. Ishii, *Chem. Pharm. Bull.*, 2005, **53**, 100.
9 J. Calzavara and J. McNulty, *Tetrahedron Lett.*, 2011, **52**, 5672.
10 (*a*) K. Biswajit, C. B. Nabin, B. Maitreyee and B. Ghanashyam, *Synlett*, 2001, **9**, 1411; (*b*) K. Srinivas, S. R. Reddy, M. R. Rao, I. Babu, K. Vinigari, R. S. Kumar, S. Rangineni, A. Tummala, J. Iqbal, S. Oruganti and B. Kandagatla, *PCT Int. Appl.*, WO 2012146980, 2012.
11 Overall atom economy of the route: 35.8%.