Available online at www.sciencedirect.com
ScienceDirect
Journal of Pharmaceutical and Biomedical Analysis 43 (2007) 1161–1163
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Short communication

Isolation and characterisation of impurities in adapalene

Elisabetta Brenna *, Samuele Frigoli, Giovanni Fronza, Claudio Fuganti, Federico Sala

Dipartimento di Chimica, Materiali ed Ingegneria Chimica del Politecnico, Istituto CNR per la Chimica del Riconoscimento Molecolare, Via Mancinelli 7, I-20131 Milano, Italy

Received 17 July 2006; accepted 24 September 2006
Available online 13 November 2006

Abstract

Three impurities of structure **2**–**4** were isolated and characterised during the optimisation of a synthetic procedure to adapalene. Impurity **1** was a by-product of the Friedel–Crafts reaction of adamantanol with 4-bromoanisole. Impurities **3** and **4** were due to side reactions of the final Negishi coupling.

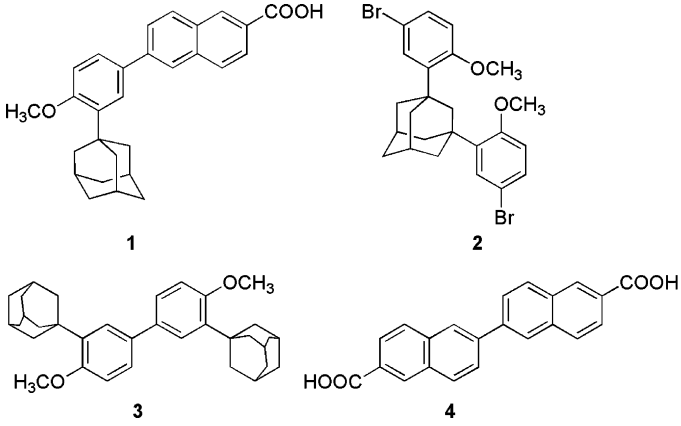
Keywords: Adapalene; Impurity; Isolation; Structural characterisation

1. Introduction

Retinoids, *i.e*. natural and synthetic analogues of Vitamin A, are known to play a key role in controlling cell proliferation and differentiation [1]. This class of substances has a great potential for the treatment of several hyperproliferative diseases. *All-trans* retinoic acid, 13-*cis*-retinoic acid and synthetic analogues are widely employed in the management of dermatological diseases such as acne and psoriasis [2]. The retinoids are also under study for the treatment and prevention of some forms of cancer, including the acute promyelocytic leukaemia [3].

Structural modifications of the retinoid skeleton led to the identification [4] of the 4-substituted-3-(1-adamantanyl)phenyl moiety as a new pharmacophore to replace the β-cyclogeranylidene ring of the naturally occurring *all-trans* retinoic acid. For example, adapalene (**1**) is effective in the treatment of acne, psoriasis and photoaging [5] and since 1996 it has been used as a topical drug under the trade name of Differin [6].

Recently, we were involved in the optimisation of the synthetic sequence of adapalene **1**, according to Charpentier's procedure [4,7]. We isolated and characterized impurities **2**–**4**. We now wish to report on the elucidation of the chemical structure of these three by-products, which are strictly related to the reactions employed in this specific synthetic path.



2. Experimental

2.1. Mass spectrometry

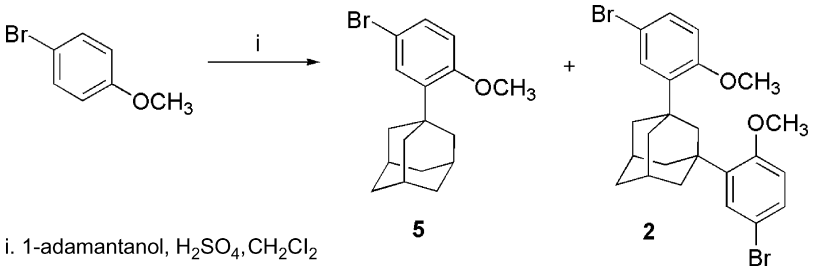
The ESI spectra were acquired on a Bruker Esquire 3000plus instrument. GC–MS analyses were performed on a HP 6890 gas chromatograph equipped with a 5973 mass-detector, using a HP-5MS column (30 m × 0.25 mm × 0.25 μm). The following temperature program was employed: 60° (1 min)/6°/min/150° (1 min)/12°/min/280° (8 min)/5°/min/300 (5 min).

2.2. NMR spectroscopy

^{1}H and ^{13}C NMR spectra were acquired on a Bruker DMX instrument at 305 K. The hydrogen and carbon chemical shifts

* Corresponding author. Tel.: +39 02 23993077; fax: +39 02 23993080.
E-mail address: elisabetta.brenna@polimi.it (E. Brenna).

0731-7085/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.jpba.2006.09.035



Scheme 1.

are referred to the internal tetramethylsilane (TMS). The coupling constants are expressed in Hertz.

2.3. Isolation of the impurities

2.3.1. Impurity **2** *[1,3-bis(5-bromo-2-methoxyphenyl)adamantane]*

Impurity **2** was isolated by silica gel column chromatography of the reaction residue obtained by stirring a mixture of 4-bromo anisole (0.20 mol), 1-adamantanol (0.22 mol), and concentrated sulphuric acid (10 ml) in CH_2Cl_2 (350 ml) at r.t. for 24 h. Elution with hexane/ethylacetate 7/3 allowed the recovery of impurity **2** (R_f 0.25).

^{1}H NMR ($CDCl_3$) δ (ppm): 7.32 (2H, d, $J = 2.2$ Hz, H–C(6) of the aromatic rings), 7.26 (2H, dd, $J = 8.5$ and 2.2 Hz, H–C(4) of the aromatic rings), 6.73 (2H, d, $J = 8.5$ Hz, H–C(5) of the aromatic rings), 3.80 (6H, s, $2OCH_3$), 2.35 (2H, br s, adamantane hydrogens), 2.25 (2H, br s, adamantane hydrogens), 2.19 (4H, br d, $J = 12$ Hz, adamantane hydrogens), 1.95 (4H, br d, $J = 12$ Hz, adamantane hydrogens), 1.76 (2H, br s, adamantane hydrogens). ^{13}C NMR ($CDCl_3$) δ (ppm): 157.9, 140.3, 129.9, 129.4, 113.4, 113.3, 55.2, 42.1, 39.8, 38.1, 36.4, 29.6; GC/MS *m/z*: 508 ($M^+ + 4$, 50), 506 ($M^+ + 2$, 100), 504 (M^+, 50), 281 (35), 207 (55).

2.3.2. Impurity **3** *[3,3′-diadamantyl-4,4′-dimethoxybiphenyl]*

Crystallisation of compound **9** from hexane-ethyl acetate 1/1 gave mother liquors containing 10% (^{1}H NMR) of impurity **3**. The mother liquors were chromatographed on a silica gel column using hexane/ethyl acetate 95/5 as an eluent, to afford an analytical sample of impurity **3**.

^{1}H NMR ($CDCl_3$) δ (ppm): 7.41 (2H, d, $J = 2.4$ Hz, H–C(2) of the aromatic rings), 7.36 (2H, dd, $J = 8.3$ and 2.4 Hz, H–C(6) of the aromatic rings), 6.93 (2H, d, $J = 8.3$ Hz, H–C(5) of the aromatic rings), 3.88 (6H, s, $2OCH_3$), 2.17 (12H, br d, $J = 3$Hz, adamantane hydrogens), 2.10 (6H, br s, adamantane hydrogens), 1.81 (12H, br d, $J = 3$Hz, adamantane hydrogens). MS (ESI, positive ions): *m/z* 482 (M^+).

2.3.3. Impurity **4** *[2,2′-binaphthyl-6,6′-dicarboxylic acid]*

Crystallisation of the triethylammonium salt of adapalene from ethanol (**1**) allowed us to recover mother liquors containing 7% (^{1}H NMR) of impurity **4**.

^{1}H NMR (DMSO d_6) δ (ppm): 12.35 (1H, br s, COOH), 8.66 (2H, d, $J = 1.7$ Hz), 8.51 (2H, d, $J = 2.0$ Hz), 8.27 (2H, d, $J = 8.8$ Hz), 8.14 (2H, d, $J = 8.8$ Hz), 8.13 (2H, dd, $J = 8.8$ and 2.0 Hz), 8.09 (2H, dd, $J = 8.8$ and 1.7 Hz). MS (ESI, negative ions): *m/z* 341 $[M - H]^-$.

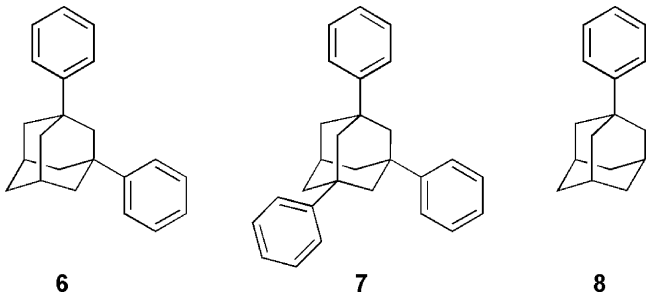
3. Results and discussion

We first discovered the formation of an interesting and unexpected impurity in the Friedel–Crafts reaction of 1-adamantol with 4-bromoanisole in methylene chloride in the presence of sulfuric acid (Scheme 1). The analytical and spectroscopic data led us to draw structure **2** for this impurity of the main desired product **5**. We were very surprised by this result and a search in the literature highlighted the following details on the reactivity of the adamantane skeleton.

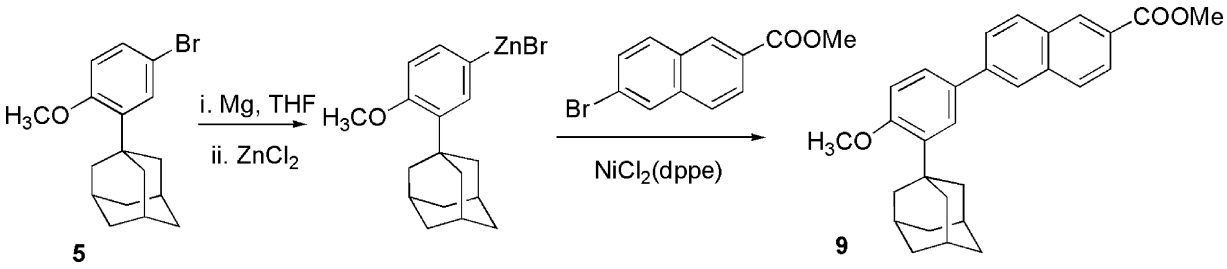
In 1972 Newman reported [8] on the possibility of preparing 1,3-diphenyl (**6**) and 1,3,5-triphenyladamantane (**7**) by heating 1-bromoadamantane in refluxing benzene in the presence of *t*-butyl bromide and 1/12 molar equivalent of aluminum chloride (Scheme 2). In the absence of *t*-butyl bromide, 1-phenyladamantane (**8**) and 1,3-diphenyladamantane (**6**) were obtained in 2:1 ratio. No explanation of the mechanism was given.

In 1985 Laszlo reported [9] on the multiple chlorination and arylation at the tertiary positions of adamantane by treatment of adamantane itself with $FeCl_3$-doped K10 montmorillonite in CCl_4 or in aromatic solvents. It was suggested a mechanism, involving the formation of tertiary adamantyl cation directly from adamantane. All these data are consistent with our finding, *i.e.* with a second Friedel–Crafts reaction involving 4-bromoanisole and the tertiary carbocation directly obtained from **5** (See Scheme 1).

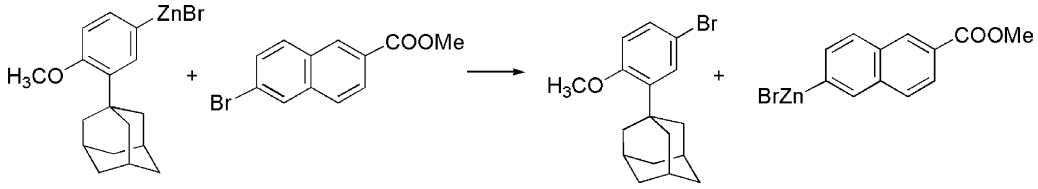
The other two side products **3** and **4** were found in the biaryl product **9**, obtained by nickel mediated coupling of methyl bromonaphthoate with the zinc organic prepared from the adamantyl substituted bromo derivative **5** (Scheme 3).



Scheme 2.



Scheme 3.



Scheme 4.

Crystallisation of **9** allowed us to recover impurity **3** from the mother liquors. Structure **3** was assigned on the basis of NMR and MS spectra.

Crystallisation of the triethylammonium salt of adapalene allowed the recovery of mother liquors enriched in the impurity to which structure **4** could be attributed by means of NMR and MS spectra analyses.

The accepted mechanism for the Negishi coupling [10] consists of the following steps: oxidative addition of the bromo arene to the transition metal complex (*i.e.* in this case methyl bromonaphthoate), transmetalation of the zinc organic and insertion of the second aryl moiety in the coordination sphere of the transition metal (*i.e.* in this case the adamantyl substituted benzene derivative), reductive elimination with the formation of the biaryl product. According to this mechanism, cross-homo scrambling due to halogen–metal exchange (Scheme 4) could afford homocoupled materials, such as **3** and **4**.

4. Conclusions

Impurities **2**–**4** are due to side reactions occurring in this specific procedure to adapalene. Compound **2** is formed during the Friedel–Crafts step employed to prepare intermediate **5**. Compounds **3** and **4** are formed during the Negishi coupling. They can be present in the impurity profile of adapalene and they are quite diagnostic of the involvement of these steps in the corresponding synthetic procedure.

References

[1] L.J. Gudas, M.B. Sporn, A.B. Roberts, in: M.B. Sporn, A.B. Roberts, D.S. Goodman (Eds.), The Retinoids, Biology, Chemistry and Medicine, Raven Press, New York, 1994, pp. 443–520.
[2] A.S. Boyd, Am. J. Med. 86 (1989) 568–574.
[3] C. Chomienne, P. Ballerini, N. Balitrand, M. Amor, J.F. Bernard, P. Boivin, M.T. Daniel, R. Berger, S. Castaigne, L. Degos, Lancet ii (1994) 746–747.
[4] B. Charpentier, J.-M. Bernardon, J. Eustache, C. Millois, B. Martin, S. Michel, B. Shroot, J. Med. Chem. 38 (1995) 4993–5006.
[5] B. Shroot, S. Michel, J. Am. Acad. Dermatol. 36 (1997) S96–S103.
[6] (a) B. Shroot, J. Eustache, J.M. Bernardon, U.S. Patent 4,717,720, 1988.; (b) B. Shroot, J. Eustache, J.M. Bernardon, EP 199636 B1, 1989.
[7] Z. Liu, L. Xiang, Org. Process. Res. Dev. 10 (2006) 285–288.
[8] H. Newman, Synthesis (1972) 692–693.
[9] S. Chalais, A. Cornelis, A. Getsmans, W. Kolodziejski, P. Laszlo, A. Mathy, P. Metra, Helv. Chim. Acta 68 (1985) 1196–1203.
[10] E. Negishi, Acc. Chem. Res. 15 (1982) 340–348.