RESEARCH LETTER

Concise synthesis of the retinoic acid receptor (RAR) agonist AGN-193836 utilizing a photochemical benzylic oxidation

Paul V. Fish and Michael J. Ralph*

Regenerative Medicine Chemistry, Worldwide Medicinal Chemistry, Pfizer Global Research & Development, Ramsgate Road, Sandwich Kent CT13 9NJ, UK

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A new, concise synthesis of retinoic acid receptor (RAR)-α agonist AGN-193836 (1) is described which employs a photochemical benzylic methyl oxidation with molecular oxygen as the key step (3 → 2). Further this route explores the application of green photochemistry in the synthesis of drug candidates and avoids a number of toxic or highly pyrophoric reagents that had been described in previous syntheses of 1. In addition, the oxidation proved to be higher yielding when compared to potassium permanganate, a metal oxidant typically used for this –CH₃ to –CO₂H functional group conversion.

Keywords: AGN-193836; benzylic oxidation; photochemistry; Friedel-Crafts alkylation

Introduction

Retinoic acid receptor (RARs) and rexinoid X receptors (RXR) play a key role in the regulation of cell growth and survival and so have utility in treating a number of diseases including cancer and metabolic disorders (1). There has been considerable interest in discovering subtype selective RAR and RXR (each have three subtypes α, β, and γ) agonists in order to tease apart the pharmacological role and safety liabilities of each subtype and to identify improved second generation drug candidates suitable for clinical studies (2).

Our interest was in the evaluation of subtype selective RAR and RXR agonists for promoting neuroregeneration (3, 4) and decided to create a ‘toolbox’ of suitable RAR and RXR agonists for use in biological experiments (5). A search of the literature identified AGN-193836 (1) as a potent, selective RAR-α agonist which was assessed to be a suitable ‘chemical probe’ for evaluating the role of RAR-α (6, 7). Appraisal of AGN-193836 (1) in a number of pre-clinical disease models required the synthesis of multi-gram quantities of 1.

The challenge of creating the molecular architecture of 1 has led to a number of noteworthy syntheses (6–9). Chandraratna et al. employed a methoxy methyl (MOM) protecting group strategy coupled with a lithium–halogen exchange reaction using tert-butyllithium followed by quenching with carbon dioxide to furnish the carboxylic acid (6, 7). Subsequently, Beard et al. disclosed a related synthesis...
without the need of a MOM protecting group strategy and instead used a bromo anisole to mask the phenolic group (8). However, this synthesis does still require the use of pyrophoric tert-butyllithium for installation of the carboxylic acid. In a conceptually different approach, Benbrook et al. described a synthesis of acid 2 in a 2-step acylation sequence in moderate yield (9).

In this Letter, we disclose a new and highly efficient synthesis of selective RAR-α agonist AGN-193836 (1). Our approach to 1 employed a photochemical benzylic methyl oxidation of 3 with molecular oxygen to yield tetra substituted benzoic acid 2 as the key step (Figure 1). This route was attractive to us as it would further explore the application of green photochemistry in the synthesis of drug candidates (10) and avoided a number of toxic or highly pyrophoric reagents that had been described in previous syntheses of 1. In addition, the oxidation proved to be higher yielding when compared to potassium permanganate, a metal oxidant typically used for this −CH₃ to −CO₂H functional group conversion.

Results and discussion

The substrate for the photochemical oxidation, tetralin 3, was prepared in one step and high yield from readily available starting materials. A double Friedel-Crafts alkylation of 2-methyl anisole (4) with 2,5-dichloro-2,5-dimethylhexane (5) gave 3 in near quantitative yield. The product 3 was simply isolated by extractive work-up without the need for chromatography and the reaction could be reliably performed on multi-gram scale (Scheme 1).

Our initial attempts at the photochemical oxidation of the benzylic methyl group of 3 followed the method as first described by Sugai and Itoh (11). Irradiation of a solution of 3 in ethyl acetate with a 400 W mercury lamp in the presence of allyl bromide (0.3 equiv) under an atmosphere of oxygen gave the required benzoic acid 2 in high yield (Scheme 1). The progress of the reaction was monitored by HPLC-MS where the consumption of starting material 3, formation of the intermediate aldehyde 6 and then benzoic acid 2 were observed. The aldehyde 6 was formed for the first eight hours of irradiation at which point benzoic acid 2 began to appear. The amount of acid 2 steadily rose while the amount of aldehyde 6 remained relatively constant until all the starting material 3 was consumed. Complete conversion through to acid 2 was reached after 48 hours of irradiation. The isolation of acid 2 was achieved by extraction into base followed by acidification to give 2 as a yellow solid with an isolated yield of 95%. This photochemical oxidation has been performed on 1 g scale.

In order to accelerate the rate of reaction and optimize yield of product formation, the following equipment and experimental techniques were employed: (1) the reaction solution was purged with oxygen gas for several minutes prior to irradiation; (2) the reaction vessel was jacketed with a cooling water condenser; (3) CAUTION: If a balloon of oxygen gas is used rather than a gentle flow of gas (recommended), it is important to protect the balloon from bursting as a result of photo degradation. This can be accomplished by siting the oxygen balloon in an adjacent vented fume cupboard and connecting to the reaction vessel with plastic tubing.

The oxidation of 3 to acid 2 was also performed with potassium permanganate in order to compare the photo oxidation procedure with a traditional metal oxidant. Reaction of 3 with KMnO₄ in aqueous sodium hydroxide/pyridine at reflux gave acid 2 in 42% isolated yield (Scheme 1).

The conversion of acid 2 to 1 is outlined in Scheme 2, where the difluorobenzamide is installed, the 3-phenol unmasked and the 4-bromine atom is introduced. Activation of 2 in situ with SOCl₂ gave the corresponding acid chloride followed by reaction with
ethyl 4-amino-2,6-difluorobenzoate gave amide 7 in good yield. Demethylation of 7 with boron tribromide in dichloromethane gave free phenol 8 in quantitative yield and then bromination with bromine in acetic acid furnished 9. The synthesis of AGN-193836 was concluded with simple base hydrolysis of 9 with lithium hydroxide to yield benzoic acid 1.

**Experimental**

**Hazards**

The medium pressure mercury lamp (400 W) produces an intense, bright light and significant heat which requires suitable shielding.

**Representative photo oxidation procedure**

3-Methoxy-5,5,8,8-tetramethyl-6,7-dihydronaphthalene-2-carboxylic acid (2). Allyl bromide (110 μL, 1.29 mmol, 0.3 equiv.) was added to a solution of tetralin 3 (1.00 g, 4.3 mmol) in EtOAc (20 mL) and the solution purged with oxygen gas for several minutes. The mixture was then irradiated with a 400 W medium pressure mercury lamp under an atmosphere of oxygen gas. The reaction mixture was intermittently purged with oxygen gas during the course of the reaction and the progress of the reaction was monitored by HPLC-MS where the complete conversion through to acid 2 was reached after 48 hours of irradiation. The solvents were then evaporated and the residue portioned between aqueous NaOH (2 M) and Et₂O. The aqueous phase was separated, washed with Et₂O, acidified with HCl (2 M) and extracted with EtOAc. The combined organic extracts were dried (MgSO₄) and evaporated to afford 2 (1.07 g, 4.07 mmol, 95%) as a yellow solid. ¹H (400 MHz, CDCl₃) δ 10.70 (br, 1H), 8.11 (s, 1H), 6.90 (s, 1H), 4.03 (s, 3H), 1.71–1.80 (m, 4H), 1.29 (s, 6H), 1.27 (s, 6H); LCMS (ES) m/z 263 (MH⁺).

**Conclusion**

An efficient six step synthesis of AGN-193836 has been developed enabling the synthesis of multi-gram quantities of material for biological profiling. This new synthesis employs a photochemical benzylic methyl oxidation with molecular oxygen as the key step (3 → 2) which represents a green alternative to the more common metal mediated approaches.

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