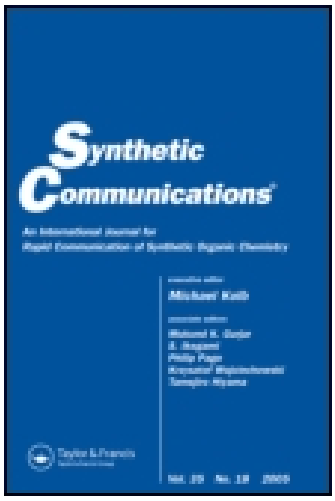

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Stephen Challenger [a] , Andrew Derrick [a] & Terry V. Silk [a]

[a] Pfizer Global Research & Development , Sandwich, Kent, CT13 9NJ, UK

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THE SYNTHESIS OF *GEM*-CYCLOPENTYL SUBSTITUTED GLUTARATES VIA THE OXIDATIVE RING CONTRACTION OF 2-ACETYLCYCLOHEXANONES

Stephen Challenger,* Andrew Derrick, and Terry V. Silk

Pfizer Global Research & Development,
Sandwich, Kent, CT13 9NJ, UK

ABSTRACT

A two step synthesis of differentially protected *gem*-cyclopentyl glutarates has been developed from 2-acetylcyclohexanone and acrylates. The key step involves an oxidative ring contraction reaction with hydrogen peroxide. The methodology has been used to prepare intermediates used in the preparation of the atriopeptidase inhibitor candoxatril.

Key Words: Oxidative ring-contraction; Hydrogen peroxide; Preparation of cyclopentyl substituted glutarates

In the early stages of a programme directed at designing synthetic routes to the atriopeptidase inhibitor candoxatril **1**[1] (Sch. 1), we required

*Corresponding author. E-mail: stephen_challenger@sandwich.pfizer.com

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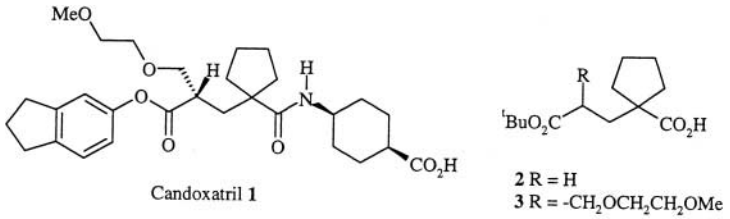
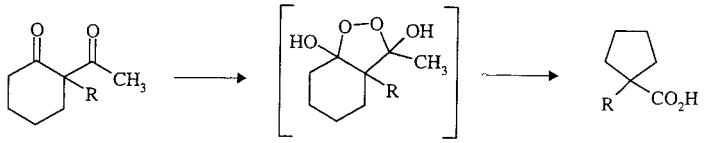


Scheme 1.



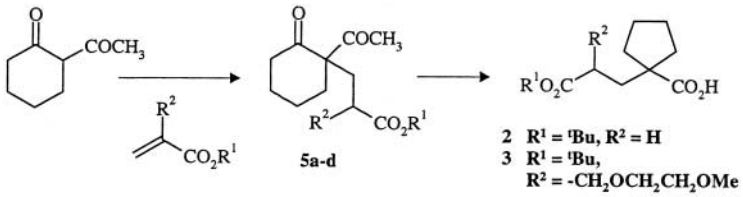
Scheme 2.

an efficient method for the preparation of the *gem*-cyclopentyl substituted glutarates **2** and **3**.

In the original synthesis of candoxatril, the key intermediate **2** was prepared in less than 40% yield by the direct alkylation of the lithium dianion of cyclopentanecarboxylic acid with *tert*-butyl 3-bromopropionate.[2] We required a higher yielding, more economic synthesis of **2** and **3** that avoided the use of expensive dianion chemistry.

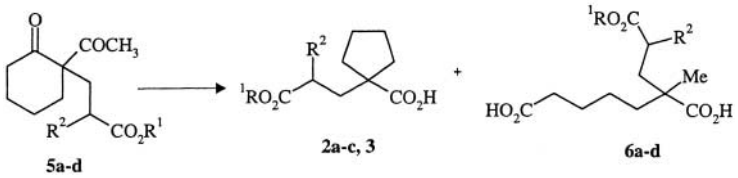
The oxidative rearrangement of 2-acylcyclohexanones with hydrogen peroxide has been reported in the literature as a method for the preparation of substituted cyclopentanecarboxylic acids.[3–6] This chemistry was used by Payne[4] to prepare alkyl substituted cyclopentanecarboxylic acids and he proposed a mechanism for the reaction involving ring contraction of the cyclic peroxide intermediate **4** (Sch. 2). A literature survey of this reaction revealed that the substrates reported to date have been either unsubstituted 2-acylcyclohexanones (R=H, Sch. 2),[4] part of a spiro-diketone[3,5] or substituted with an unfunctionalised alkyl group.[4,6] We were interested in applying this reaction to substrates containing a carboxyethyl group ($R = -CH_2CH_2CO_2R$, Sch. 2) to establish if this chemistry could be extended to the preparation of differentially protected glutarate derivatives of types **2** and **3**.

The availability of the required diketones **5** (Sch. 3)[7,8] through the Michael reaction of commercially available 2-acetylcyclohexanone with



Scheme 3.

Table 1. Reaction of Substituted 2-Acetylcyclohexanones with Hydrogen Peroxide



Entry	Substrate	Conditions	Products/Yield[a]
1	**5a** R^1=^{t}Bu, R^2=H	30% aqueous H_2O_2, H_2SO_4 (cat), *t*-BuOH rt 16 h	**2a** 78% **6a** 7%
2	**5b** R^1=Bn, R^2=H	30% aqueous H_2O_2, H_2SO_4 (cat), *t*-BuOH rt 20 h	**2b** 72%[b]
3	**5c** R^1=Et, R^2=H	30% aqueous H_2O_2, H_2SO_4 (cat), *t*-BuOH rt 24 h	**2c** 67%[b]
4	**5d** R^1=^{t}Bu, R^2=$-CH_2OCH_2CH_2OMe$	30% aqueous H_2O_2, H_2SO_4 (cat), *t*-BuOH rt 24 h	**3** 72%[c]

[a]All yields correspond to purified material. [b]Heptanedioic acid major impurity in reaction but not isolated. [c]Product isolated as crystalline isopropylamine salt.

inexpensive acrylates was an attractive feature of this approach. It is noteworthy that inexpensive hydroxide, carbonate or alkoxide bases can be used in this reaction instead of expensive lithium diisopropylamide used in the original dianion chemistry. A series of substituted 2-acetylcyclohexanones (**5a–d**, Sch. 3 and Table 1) were prepared using the method of Yanovskaya et al.[9] The crude products **5a–d** were obtained as oils and were used directly in the next step without purification.

With the required substrates **5** in hand, we investigated the key oxidative ring contraction reaction with hydrogen peroxide (CAUTION: all reactions involving hydrogen peroxide and organo-peroxide intermediates

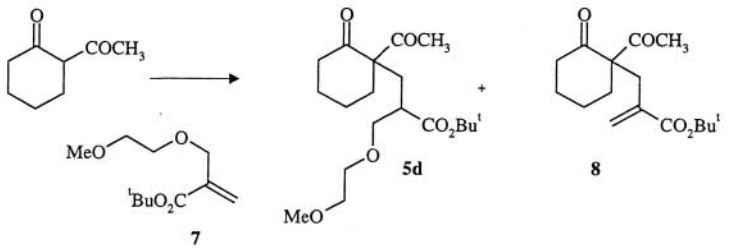
should be conducted behind a safety shield[10]) (Table 1). Acid or base catalysis was used since this type of reaction has been reported to be slow under neutral conditions.[4]

Treatment of substrate **5a** with a 30% aqueous solution of hydrogen peroxide and sulfuric acid catalyst in *t*-butanol gave the desired glutarate **2a** in 78% yield after chromatography (Entry 1). The heptanedioic acid **6a** was also isolated in 7% yield, and is believed to arise from the alternative fragmentation of the proposed peroxide intermediate **4**.[4] This impurity can readily be purged by selective extraction into aqueous base. The presence of the ester side chain in substrates **5a–d** did not interfere with oxidative ring contraction chemistry and similar yields were obtained compared with those reported for simple alkyl substituted 2-acylcyclohexanones.

A base-catalysed oxidative ring contraction reaction on substrate **5a** gave the desired product but in lower yield. Also, sodium perborate tetrahydrate in acetic acid and sodium percarbonate in *t*-butanol can be successfully used as alternative sources of hydrogen peroxide in this reaction, although the yields are lower compared with the acid-catalysed process using aqueous hydrogen peroxide. In this sequence of reactions the enolate of 2-acetylcyclohexanone can be regarded as a synthetic equivalent of the cyclopentanecarboxylic acid dianion.

The methodology has been successfully applied to the preparation of the more highly substituted glutarate **3** (Table 1, Entry 4) containing a 2-methoxyethoxy methyl (MEM) side chain. A problem with this synthesis was a low yielding Michael addition reaction to prepare diketone **5d** (Sch. 4), due to competing β-elimination of 2-methoxyethanol to give acrylate **8**.

An extensive investigation of base and solvent combinations led to the discovery of optimised conditions for this reaction involving catalytic potassium *t*-butoxide in acetonitrile at −10°C. The Michael adduct **5d** was obtained from 2-acetylcyclohexanone and acrylate **7**[2b] in 55% yield after chromatography.



Scheme 4.

In summary, we have developed an efficient two step synthesis of the differentially protected *gem*-cyclopentyl glutarates **2** and **3** from commercially available and inexpensive 2-acetylcyclohexanone and acrylates. The key step, involving an oxidative rearrangement of a substituted 2-acetylcyclohexanone, has been demonstrated in substrates with side chains containing ester functionality. The methodology has been used to prepare intermediates used in the preparation of the atriopeptidase inhibitor candoxatril.

EXPERIMENTAL

Melting points were determined on a Electrothermal melting point apparatus and are uncorrected. 300 MHz ^{1}H NMR and 75 MHz ^{13}C NMR spectra were recorded in $CDCl_3$. Chemical shifts are reported in ppm (δ) relative to residual protons in the deuterated solvent. Analytical thin-layer chromatography (TLC) was carried out using commercial glass-backed Merck, Silica gel 60, F_{254} plates. All materials obtained from commercial suppliers were used without further purification.

General procedure for preparation of substituted 2-acetylcyclohexanones 5a–c:[7,8] To a suspension of 2-acetylcyclohexanone, potassium carbonate (1.2 eq) and benzyltriethylammonium chloride (0.02 eq) in toluene (2.8 mL/g) was added in one portion the appropriate acrylate (1.5 eq) at room temperature. The suspension was stirred at 40°C for 18 h, diluted with distilled water (10 mL/g) and toluene (5 mL/g) and the layers separated. The aqueous layer was extracted with toluene (3 × 5 mL/g), the combined toluene extracts dried over magnesium sulfate, filtered and concentrated in vacuo to give the desired substituted 2-acetylcyclohexanone **5a–c**. The crude products were used without further purification.

2-Acetyl-2-[2-(*tert*-butoxycarbonyl)-3-(2-methoxyethoxy)-propyl]cyclohexanone (5d): To a suspension of 2-acetylcyclohexanone (3.5 g, 0.025 mol) and *tert*-butyl 2-(2-methoxyethoxymethyl)acrylate (5.41 g, 0.025 mol) (see Ref. [2b] for preparation) in acetonitrile (20 mL) was added in one portion, potassium *tert*-butoxide (0.14 g, 0.0012 mol) at −10°C. The mixture was stirred at −10°C for 24 h and at room temperature for 18 h. The mixture was partitioned between ethyl acetate (15 mL) and distilled water (20 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (2 × 15 mL) and the combined ethyl acetate extracts concentrated in vacuo to give a brown oil (7.52 g). The crude product was purified by chromatography on silica by eluting with *n*-hexane/ethyl acetate (4 : 1) to give the desired product **5d** as a mixture of diastereoisomers, (4.98 g, 55.8%) IR

(neat) 2980, 2935, 2870, 1720, 1695, 1450 cm^{-1}. Anal. %. Found: C, 64.22; H, 9.03. $C_{19}H_{32}O_6$ requires: C, 64.02; H, 9.05.

General procedure for the oxidative ring contraction reaction illustrated by the preparation of 2a: CAUTION: All reactions involving hydrogen peroxide and organo-peroxide intermediates should be conducted behind a safety shield.

1-[2-*tert*-Butoxycarbonyl)ethyl]-1-cyclopentanecarboxylic acid 2a: To a solution of crude 2-acetyl-2-[2-(*tert*-butoxycarbonyl)ethyl]cyclohexanone **5a** (42 g, 0.15 mol) in *tert*-butanol (84 mL) was cautiously added a 30% aqueous solution of hydrogen peroxide (21 mL, 0.187 mol) and concentrated sulfuric acid (0.25 mL, 98% w/w) at room temperature, maintaining the reaction temperature below 50°C during the addition. The mixture was stirred at room temperature for 18 h, partitioned between dichloromethane (100 mL) and water (100 mL), and the layers separated. The dichloromethane layer was washed with a 5% aqueous sodium sulfite solution (50 mL), dried over magnesium sulfate, filtered and concentrated in vacuo to give the crude product. The crude product partially crystallised on standing overnight to provide the desired compound **2a** (15.5 g), after collecting and washing with *n*-pentane. Chromatographic purification of the mother liquors on silica (ethyl acetate : *n*-hexane 1 : 10) provided a further 14.47 g of the desired compound (combined yield 29.97 g, 78%), m.p. = 89–93°C. ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 1.45–1.60 (m, 2H), 1.62–1.78 (m, 4H), 1.92–1.99 (m, 2H), 2.11–2.21 (m, 2H), 2.21–2.33 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$) δ 25.30, 28.33, 32.45, 33.74, 36.29, 53.32, 80.57, 172.99, 184.23 ppm.

The following glutarates (shown in Table 1) were prepared using this general procedure.

1-[2-(Benzyloxycarbonyl)ethyl]-1-cyclopentanecarboxylic acid 2b: IR (neat) 3800–2400, 1735, 1695, 1450 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.47–1.63 (m, 2H), 1.62–1.80 (m, 4H), 1.98–2.10 (m, 2H), 2.10–2.25 (m, 2H), 2.38–2.53 (m, 2H), 5.15 (s, 2H), 7.38–7.46 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$) δ 25.02, 31.01, 33.72, 36.69, 53.38, 66.69, 128.38, 129.06, 136.35, 173.72, 183.72 ppm. Anal. %. Found: C, 69.70; H, 7.18. $C_{16}H_{20}O_4$ requires: C, 69.55; H, 7.29.

1-[2-(Ethyoxycarbonyl)ethyl]-1-cyclopentanecarboxylic acid 2c: ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H), 1.47–1.62 (m, 2H), 1.62–1.82 (m, 4H), 1.92–2.08 (m, 2H), 2.10–2.27 (m, 2H), 2.32–2.46 (m, 2H), 4.19 (q, 2H) ppm. ^{13}C NMR ($CDCl_3$) δ 14.26, 25.15, 31.21, 33.56, 36.15, 53.21, 60.49, 173.38, 183.52 ppm.

1-[2-(*tert*-Butoxycarbonyl)-3-(2-methoxyethoxy)propyl]-1-cyclopentane carboxylic acid (3) isopropylamine salt: To a solution of 2-acetyl-2-[2-(*tert*-butoxycarbonyl)-3-(2-methoxyethoxy)propyl]cyclohexanone **5d** (5.45 g, 0.015 mol) in *tert*-butanol (10.9 mL) and concentrated sulfuric acid (one drop) was cautiously added a 30% aqueous solution of hydrogen peroxide

(2.1 mL, 0.018 mol) at room temperature. The mixture was stirred at room temperature for 24 h, partitioned between dichloromethane (20 mL) and the layers separated. The dichloromethane layer was washed with water (10 mL), the combined aqueous extract acidified to pH 2 with aqueous hydrochloric acid solution (5 M) and extracted with *n*-hexane (2 × 20 mL). The combined *n*-hexane extracts were washed with water (5 mL), concentrated under reduced pressure and azeotropically dried with ethyl acetate to give the title acid as an oil (3.99 g, 79% crude yield, 96% purity GC normalisation). R_f 0.44 (silica, ethyl acetate, 1% acetic acid). The crude acid (3.4 g, 0.01 mol) was dissolved in *n*-hexane (34 mL), and isopropylamine (0.61 g, 0.01 mol) was added at room temperature. The precipated salt was cooled to 0°C, granulated for 2 h and collected to give the title compound (3.57 g, 92% yield salt formation, 72% overall yield; HPLC main band assay 98.7%), m.p. = 84–87°C. ^{1}H NMR ($CDCl_3$): δ 1.23 (d, 6H), 1.45 (s, 9H), 1.35–1.50 (m, 2H), 1.58–1.70 (m, 4H), 1.78 (dd, 1H), 1.88 (dd, 1H), 2.05–2.19 (m, 2H), 2.60–2.69 (m, 1H), 3.28 (heptet, 1H), 3.36 (s, 3H), 3.48–3.62 (m, 6H), 5.98 (br s, 3H) ppm. ^{13}C NMR ($CDCl_3$) δ 21.99, 24.51, 24.97, 27.86, 34.64, 37.98, 43.05, 44.94, 54.57, 58.78, 69.91, 71.68, 73.48, 79.98, 174.79, 183.22 ppm. Anal. %. Found: C, 61.64; H, 10.30; N, 3.46. $C_{20}H_{39}NO_6$ requires: C, 61.67; H, 10.09; N, 3.60.

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