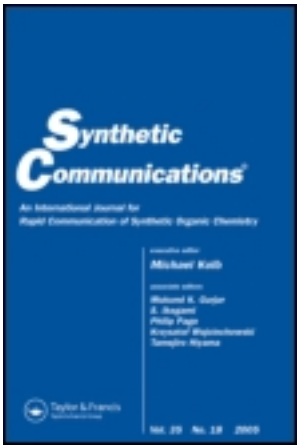

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Convenient Synthesis of Some 1,4-Disubstituted 7-Oxabicyclo[2.2.1]heptanes

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Published online: 23 Sep 2006.

To cite this article: S. R. Baker & J. R. Harris (1991) A Convenient Synthesis of Some 1,4-Disubstituted 7-Oxabicyclo[2.2.1]heptanes, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 21:20, 2015-2023, DOI: 10.1080/00397919108019807

To link to this article: http://dx.doi.org/10.1080/00397919108019807

SYNTHETIC COMMUNICATIONS, 21(20), 2015-2023 (1991)

A CONVENIENT SYNTHESIS OF SOME 1,4-DISUBSTITUTED 7-OXABICYCLO[2.2.1]HEPTANES

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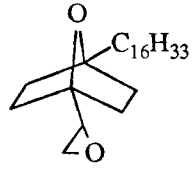
Abstract: An efficient synthesis of a 1,4-disubstituted 7-oxabicyclo[2.2.1]heptane intermediate and its subsequent conversion to a potential PAF antagonist is described.

Arising from an interest in the potential role of platelet activating factor (PAF) in allergic disease[1], we proposed a series of compounds based on 1,4-disubstituted 7-oxabicyclo[2.2.1]heptane as potential PAF antagonists. We therefore sought a facile route to the intermediate **1** which would allow easy access to the compounds we required for developing a structure-activity relationship.



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The most widely used method for preparing the 7-oxabicyclo[2.2.1]heptane ring system is by a cycloaddition to a furan and reduction of the resulting oxabicycloheptene[2]. In our case, this approach would require reaction of a 2,5-disubstituted furan with a dienophile which is known to be difficult and of which there are only a few examples in the literature[3]. We therefore adopted an alternative synthesis in which the key step was a 5-exo trigonal ring closure[4]. This procedure has the advantage of accommodating the desired substitution pattern with a minimum of functional group transformations.

The key intermediate (**1**) was derived (scheme **1**) from 1,4-cyclohexanedione mono ethylene ketal (**2**) by reaction with ethylidene triphenylphosphorane to give the olefin (**3**). Treatment of (**3**) with silica gel, pre-adsorbed with aqueous sulphuric acid[5], furnished the ketone (**4**) in high yield. A Grignard reaction in diethyl ether with hexadecylmagnesium bromide gave the alcohol (**5**) . Ring closure of (**5**) was achieved using freshly prepared N-iodosuccinimide[6] and isolation of the unstable iodooxabicyclic species (**6**) by rapid chromatographic purification on Florisil. Treatment of (**6**) with 1,8-diazabicyclo-[5.4.0]undec-7-ene gave the olefin (**7**) which required heating to 80°C with m-chloroperbenzoic acid in the presence of the radical scavenger 3-t-butyl-4-hydroxy-5-methylphenylsulphide[7] to afford the epoxide (**1**).

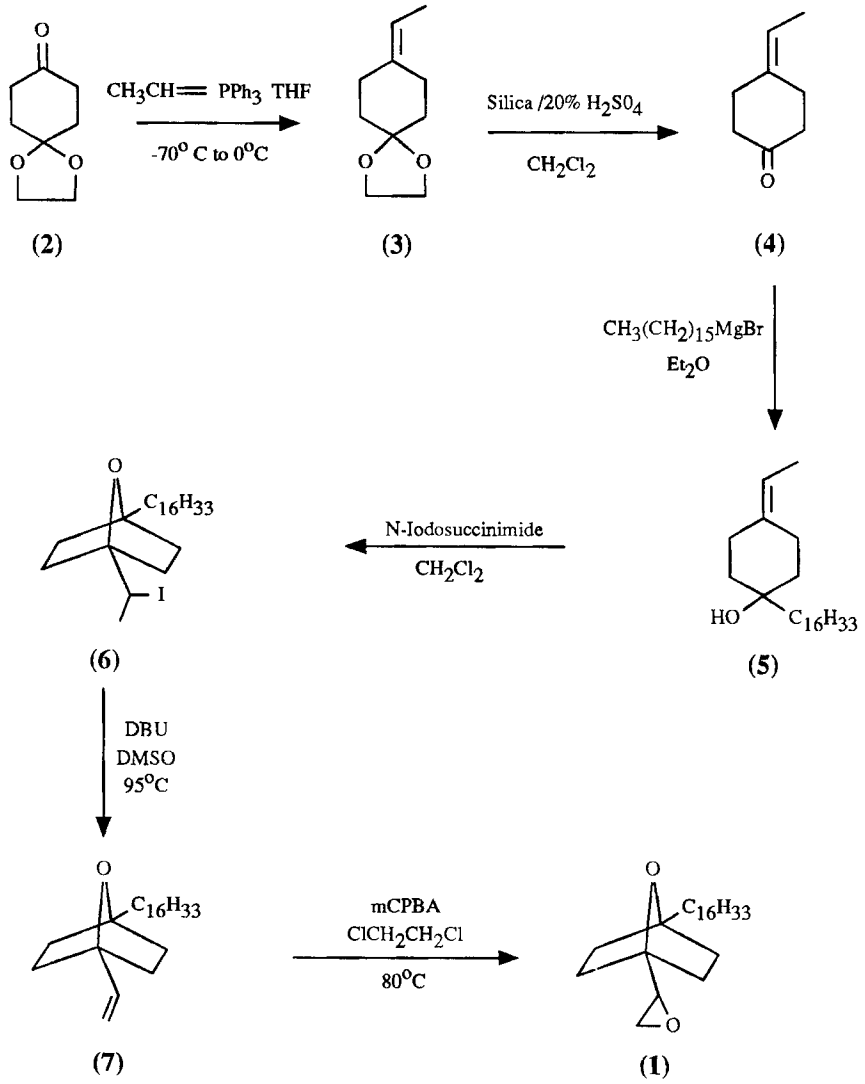
The utility of the epoxide (**1**) is demonstrated by the synthesis of the potential PAF antagonist (**11**) (scheme **2**). Regiospecific ring opening of the epoxide (**1**) with preformed benzyl alkoxide at 60°C was followed by quenching with MeI[8] to give (**8**). Debenzylation of (**8**) to give the alcohol (**9**) employed palladium on carbon as catalyst. The alcohol (**9**) was converted to the target compound (**11**) using the method of Hajdu[9].

EXPERIMENTAL

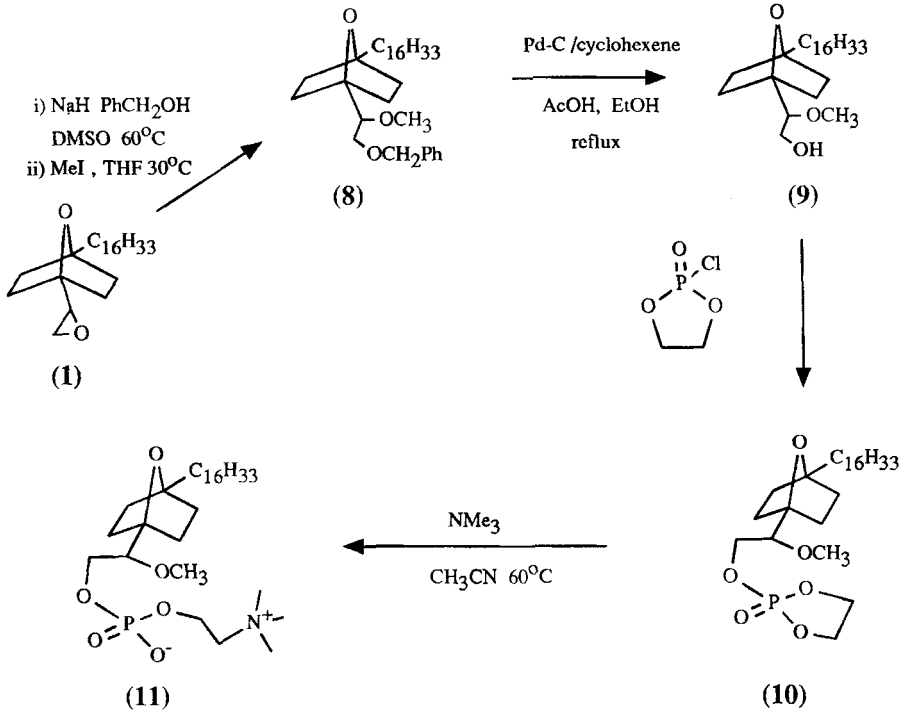
4-Ethylidenecyclohexanone ethylene acetal (3)

To a stirred suspension of ethyltriphenylphosphonium iodide (147.2 g, 0.352 mol) in THF (500 mL) at -70°C was added a solution of n-Buli (2.5 M in

SCHEME 1



SCHEME 2



hexane, 134.4 mL, 0.336 mol) dropwise. After the addition the mixture was warmed to 0°C and stirred at that temperature for 30 min. Cooling to -70°C was followed by dropwise addition of 1,4-cyclohexanedione mono ethylene acetal **(2)** (50 g, 0.32 mol) in THF (100 mL). The cooling bath was removed and stirring was continued for 24h. The reaction mixture was diluted with 1,1,2-trichlorotrifluoroethane, filtered through a pad of celite and purified by column chromatography on silica gel (eluent hexane/diethyl ether 3:2) to provide the ethylidene compound (**3**) as a colourless oil (40.05g). ^{1}H NMR ($CDCl_3$): δ 1.59 (3H,d,J=7Hz, $\underline{CH_3}$-C=C), 1.63-1.69 (4H,m,2,6-$\underline{CH_2}$), 2.22(t)

and 2.27(t) (4H,3,5-$\underline{CH_2}$), 3.96 (4H,s,O-$\underline{CH_2CH_2}$-O), 5.22 (1H,q,J=7Hz,-$\underline{CH}$=C-).

4-Ethylidenecyclohexanone (4)

A suspension of silica gel (Sorbsil C60, 150g) and aqueous sulphuric acid (20%, 20ml) in dichloromethane (400ml) was stirred for 0.5h. A solution of the ethylidene compound **(3)** (20.8g, 0.168mol) in dichloromethane (50ml) was added and the mixture stirred at room temperature for 2h. The reaction mixture was filtered and the procedure repeated by pouring the filtrate onto a prepared suspension of silica gel (100g) and aqueous sulphuric acid (15%, 20ml) in dichloromethane (200ml). After 0.5h, the reaction mixture was filtered and the solvent carefully removed under reduced pressure at room temperature to give the ketone **(4)** as a colourless oil (14.7g). ^{1}H NMR ($CDCl_3$) δ 1.65 (3H,d,J=7Hz, $\underline{CH_3}$-C=C), 2.3-2.5 (8H,m,2,3,5,6-$\underline{CH_2}$), 5.42 (1H,q,J=7Hz,$\underline{CH}$=C).

1-Ethylidene-4-hexadecyl-4-hydroxycyclohexane (5)

To a suspension of magnesium turnings (3.88g, 0.16mol) in dry diethyl ether (120ml), containing a crystal of iodine and stirred under an atmosphere of nitrogen, a solution of 1-bromohexadecane (48.74ml, 0.159mol) in dry diethyl ether (120ml) was added dropwise whilst the reaction was maintained at reflux. The suspension was stirred at room temperature for 4h, then a solution of the ketone **(4)** (16.5g, 0.133mol) in dry diethyl ether (80ml) was added dropwise at a rate which maintained a gentle reflux. The reaction mixture was stirred overnight at room temperature, washed with a saturated solution of ammonium chloride, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (eluent dichloromethane/petroleum ether (40-60°C) 1:1) to give the alcohol **(5)** as a white solid (29.8g). A small portion was crystallised from petroleum ether (40-60°C). m.p. 35-37°C. ^{1}H NMR ($CDCl_3$) δ 0.88 (3H,t,$\underline{CH_3}$-$(CH_2)_{15}$-), 1.58 (3H,d,J=7Hz,$\underline{CH_3}$-C=C-), 1.25 (30H,m,-$(\underline{CH_2})_{15}$-), 1.4-1.7 (4H,m,3,5-$\underline{CH_2}$),

2.02 (1H,dt) and 2.14 (1H,td) and 2.3 (2H,m) 2,6-$\underline{CH_2}$, 5.18 (1H,q,J=7,-$\underline{CH}$=C-).

1-Hexadecyl-4-(1-iodoethyl)-7-oxabicyclo[2.2.1]heptane (6)

To freshly prepared N-iodosuccinimide (22.04g, 0.098mol) was added a solution of the alcohol **(5)** (29.8g, 0.085mol) in dichloromethane (200ml). The resulting solution was stirred at room temperature for 2.5h under an atmosphere of nitrogen with the exclusion of light. The reaction mixture was then washed with aqueous sodium metabisulphite (10%), water and brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude oil was purified by column chromatography on Florisil (eluent petroleum ether (40-60°C)) to give the bicyclic compound **(6)** as a colourless oil (28.2g). ^{1}H NMR ($CDCl_3$) δ 0.88 (3H,t,$\underline{CH_3}$-$(CH_2)_{15}$), 1.25 (30H,m,$(\underline{CH_2})_{15}$-CH_3), 1.5- 1.9 (8H,m,2,3,5,6-$\underline{CH_2}$), 1.91 (3H,d,J=7Hz,$\underline{CH_3}$-C-I), 4.48 (1H,q,J=7Hz,-$\underline{CH}$-I). ^{13}C NMR ($CDCl_3$) (using DEPT 135 to assess multiplicity) δ 88.3, 88.5 (C-O, quaternary), 31.5 (-CH-I, methine).

1-Ethenyl-4-hexadecyl-7-oxabicyclo[2.2.1]heptane (7)

A stirred solution of the iodobicyclic compound **(6)** (14.21g, 29.8mmol) in dry DMSO (100ml) was heated under an atmosphere of nitrogen in the dark at 80-85°C with 1,8-diazabicyclo[5.4.0]undec-7-ene (7.3ml, 48.9mmol) and hydroquinone (10mg) for 16h. The reaction mixture was cooled, aqueous hydrochloric acid (2M, 500ml) was added and the mixture extracted with petroleum ether (40-60°C)/diethyl ether 95:5 (200ml). The organic phase was separated and washed with water, aqueous sodium metabisulphite (10%), brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the olefin **(7)** as a pale yellow oil (9.12g). ^{1}H NMR ($CDCl_3$) δ 0.88 (3H,t,$\underline{CH_3}$-$(CH_2)_{15}$), 1.25 (30H,m,-$(\underline{CH_2})_{15}$-CH_3), 1.5-1.9 (8H,m,2,3,5,6-$\underline{CH_2}$), 5.17 (1H,d,J=10Hz) and 5.27 (1H,d,J=18Hz) -C=$\underline{CH_2}$, 6.22 (1H,dd,J=10,18Hz,-$\underline{CH}$=C).

1-(1,2-Epoxyethyl)-4-hexadecyl-7-oxabicyclo[2.2.1]heptane (1)

A solution of the olefin (**7**) (1.86g, 5.31mmol) and m-chloroperbenzoic acid (1.19g, 6.89mmol) in 1,2-dichloroethane (50ml) was heated in the presence of 3-t-butyl-4-hydroxy-5-methylphenylsulphide (10mg) at 80°C for 3h. The reaction mixture was cooled, washed sequentially with aqueous sodium metabisulphite (20%), a saturated solution of sodium bicarbonate, water and brine then dried ($MgSO_4$), filtered and evaporated under reduced pressure to give an oil which crystallised on standing. Recrystallisation from ethanol gave the epoxide (**1**) as a white solid (1.2g), m.p. 43-45°C. ^{1}H NMR ($CDCl_3$) δ 0.88 (3H,t,$\underline{CH_3}$-$(CH_2)_{15}$-), 1.25 (30H,m,-$(\underline{CH_2})_{15}$-CH_3), 1.5-1.9 (8H,m,2,3,5,6-$\underline{CH_2}$), 2.67 (1H,dd,J=3,4Hz) and 2.83 (1H,dd,J=4,4Hz,$\underline{CH_2}$(epoxide)), 3.27 (1H,dd,J=3,4Hz,-$\underline{CH}$-(epoxide)).

1-(2-Benzyloxy-1-methoxyethyl)-4-hexadecyl-7-oxabicyclo[2.2.1]heptane (8)

To a stirred suspension of NaH (60% dispersion in oil, 55mg, 1.37mmol) in dry DMSO (5ml), was added benzyl alcohol (0.14ml, 1.37mmol). The reaction mixture was heated at 60°C under an atmosphere of nitrogen for 0.75h, followed by dropwise addition of the epoxide (**1**) (0.25g, 0.68mmol) in dry THF (5ml). The temperature was maintained at 60°C for 4h then at 40°C for 16h before being cooled to room temperature and treated with methyl iodide (0.22ml, 3.4mmol). The reaction mixture was stirred at room temperature for 6h, after which water (30ml) was added. After extraction with petroleum ether (40-60°C)/diethyl ether 9:1 (2x), the combined extracts were washed with water and brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica (eluent petroleum ether (40-60°C)/diethyl ether 98:2, 95:5) to give (**8**) as a colourless oil (0.26g). ^{1}H NMR ($CDCl_3$) δ 0.88 (3H,t,$\underline{CH_3}$-$(CH_2)_{15}$-), 1.25 (30H,m,-$(\underline{CH_2})_{15}$-CH_3), 1.5-1.9 (8H,m,2,3,5,6-$\underline{CH_2}$), 3.5 to 3.8 (3H,m,-$\underline{CH}(OCH_3)$-$\underline{CH_2}$-OBz), 3.55 (3H,s,O$\underline{CH_3}$), 4.54 (2H,s,O$\underline{CH_2}$Ph).

1-Hexadecyl-4-(2-hydroxy-1-methoxyethyl)-7-oxabicyclo[2.2.1]heptane (9)

A suspension of **(8)** (1.70g, 3.48mmol) and 10% palladium on carbon (0.42g) in a mixture of cyclohexene (30ml), ethanol (100ml) and acetic acid (30ml) was heated under reflux under an atmosphere of nitrogen for 70h. The reaction mixture was filtered, concentrated under reduced pressure and then diluted with petroleum ether (40-60°C). The solution was washed sequentially with a saturated solution of sodium bicarbonate, water and brine, then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica (eluent petroleum ether (40-60°C)/diethyl ether 1:1) to give the alcohol **(9)** as a colourless oil (1.25g). A sample was crystallised from ethanol as a white solid. m.p. 45-48°C. ^1H NMR ($CDCl_3$) δ 0.88 (3H,t,$\underline{CH_3}$-$(CH_2)_{15}$-), 1.25 (30H,m,-$(\underline{CH_2})_{15}$-CH_3), 1.5-1.9 (8H,m,2,3,5,6-$\underline{CH_2}$), 2.48 (1H,dd,$\underline{OH}$), 3.5-3.8 (3H,m,-$\underline{CH}(OCH_3)$-$\underline{CH_2}OH$), 3.55 (3H,s,-O$\underline{CH_3}$).

1-Hexadecyl-4-[1-methoxy-2-(2-oxo-1,3,2-dioxaphospholan-2-yloxymethyl)-ethyl]-7-oxabicyclo[2.2.1]heptane (10)

Dry triethylamine (0.286g, 2.83mmol) and 2-chloro-2-oxo-1,3,2-dioxaphospholane (0.40g, 2.83mmol) were added to a solution of the alcohol **(9)** (0.98g, 2.83mmol) in dry benzene. The reaction mixture was stirred under an atmosphere of nitrogen at room temperature for 2h. The precipitate of triethylamine hydrochloride was filtered and the solvent removed under reduced pressure to give a crude oil **(10)** which was used immediately in the next step.

***rac*-O-2-(4-hexadecyl-7-oxabicyclo[2.2.1]hept-1-yl)-2-methoxyethyl O-trimethylammonioethyl phosphate (inner salt) (11)**

A solution of the crude oil **(10)** (1.11g, 2.20mmol) in dry acetonitrile (2.5ml) was added to trimethylamine (1ml) contained in a reactor vial under an atmosphere of nitrogen at 0°C. The vial was sealed and heated with stirring at 60°C for 24h. The reaction mixture was cooled and the precipitate filtered, washed with dry acetonitrile and dried under reduced pressure at 50°C.

Recrystallisation from chloroform/diethyl ether gave **(11) as** a white hygroscopic solid (0.44g). ^{1}H NMR (MeOH-d_4) δ 0.89 (3H,t,$\underline{CH_3}$-$(CH_2)_{15}$), 1.2-1.4 (30H,m,-$(\underline{CH_2})_{15}$-CH_3), 1.4-1.9 (8H,m,2,3,5,6-$\underline{CH_2}$), 3.22 (9H,s,$N^+(\underline{CH_3})_3$), 3.53 (3H,s,O$\underline{CH_3}$), 3.66 (2H,t,$\underline{CH_2}N^+$), 3.65 (1H,dd,-$\underline{CH}$-OCH_3), 3.82 (1H,ddd,J=6,6,11Hz) and 4.05 (1H,ddd,J=3,5,11Hz) $\underline{CH_2}$-$CHOCH_3$, 4.29 (2H,m,-O-$\underline{CH_2}CH_2$-N^+).

Acknowledgments: We thank S. Morgan and D. Sudworth for the spectroscopic analysis. We are grateful to P. Bishop and T. Clarke for helpful discussions.

REFERENCES

1. Braquet, P., Touqui, L., Shen, T.Y., Vargaftig, B.B., *Pharmacol. Rev.*, **1987**, 39, 97.
2. Sargent, M.V. and Dean, F.M. in *"Comprehensive Heterocyclic Chemistry"*, eds. Bird, C.W. and Cheeseman, G.W.H., Pergamon Press, Oxford, **1984**, vol.4, p.237.
3. a) Potts, K.T., Walsh, E.B., *J. Org. Chem.*, **1988**, 53, 1199
   b) Mavoungou-Gomes, L., *Bull. Soc. Chim. France*, **1967**, 1764
4. Baldwin, J., J. Chem. Soc., Chem. Commun. **1976**, 734.
5. Huet, F., Lechevallies, A., Pellet, M., Conia, J. M., *Syn.* ***1978***, 63.
6. Murai, A., Tanimote, N., Sakamoto, N., Masamune, T., *J. Am. Chem. Soc.*, **1988**, 110, 1985.
7. Kishi, Y., Aratani, M., Tanino, H., Fukuyama, T., Goto, T., *J. Chem. Soc., Chem. Commun.*, **1972**, 64.
8. Inoue, K., Nomura, H., Aono, T., *European Patent Application*, EP 255,366 (29th July **1987**).
9. Hajdu, J., Bhatia, S.K., *J. Org. Chem.*, **1988**, 53, 5034.

(Received in UK 28 May, 1991)