

## Short Research Article

# Synthesis of the myoview™ ligand, (bisphosphinoethane-1,2-<sup>14</sup>C)tetrofosmin<sup>†</sup>

GEOFFREY T. WOOLLEY\*, SEAN L. KITSON and R. GORDON REID

GE Healthcare Limited, Amersham Place, Little Chalfont, Buckinghamshire HP7 9NA, UK

Received 22 August 2006; Revised 2 November 2006; Accepted 22 November 2006

**Abstract:** The carbon-14 radiolabels in [bisphosphinoethane-1,2-<sup>14</sup>C]tetrofosmin ligand were readily introduced by reacting 1,2-dibromo[U-<sup>14</sup>C]ethane with bis(2-ethoxyethyl)benzylphosphine (**1**). This was converted to the Myoview™ ligand in an overall yield of 45%. This radiosynthesis was important in obtaining marketing approval from the regulatory authorities and allowed Myoview™ to become one of the main heart imaging agents of today. Copyright © 2007 John Wiley & Sons, Ltd.

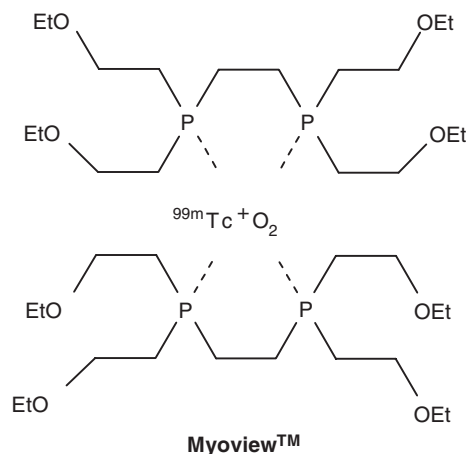
**Keywords:** Myoview™; tetrofosmin; gamma emitter; technetium-99m

## Introduction

Myoview™ is used in cardiology as an imaging agent to study the heart in microscopic detail. The cardiac imaging agent is labelled with technetium-99m complexed to a biphosphine ligand tetrofosmin or P-53. Myoview™ is useful in the diagnosis and localization of regions of reversible myocardial ischaemia in the

presence or absence of infarction under exercise and rest conditions (Figure 1).<sup>1</sup> This achievement was recognized by winning the 1998 prestigious Queens Award for Technical Achievement.<sup>2</sup> One reason for the success of Myoview™ is that it uses the gamma emitter technetium-99m rather than thallium-201.<sup>3,4</sup>

Many different phosphine ligands were prepared and tested during the development of Myoview™ and tetrofosmin was found to be the most superior ligand (Personal communication, P. G. Edwards, Department of Chemistry, Cardiff University, UK).<sup>5</sup>



## Myoview™ highlights

- Technetium-99m-labelled drug for myocardial perfusion imaging for detection of Coronary Artery Disease (CAD).<sup>6</sup>
- Indicated for use with approved pharmacologic stress agents for known or suspected CAD.<sup>6</sup>
- High target-to-background ratio provides clear images.<sup>4,6,7</sup>
- Improved image clarity provides confident diagnosis.<sup>4,8</sup>
- Demonstrates good sensitivity, specificity, and diagnostic accuracy.<sup>8</sup>
- Imaging can begin as soon as 15 minutes or up to 4 hours after administration of Myoview™, enhancing patient management and department flexibility. The product was approved by the FDA in February 1996.
- The Myoview™ is supplied as a kit containing tetrofosmin, tin chloride and sodium hydrogen

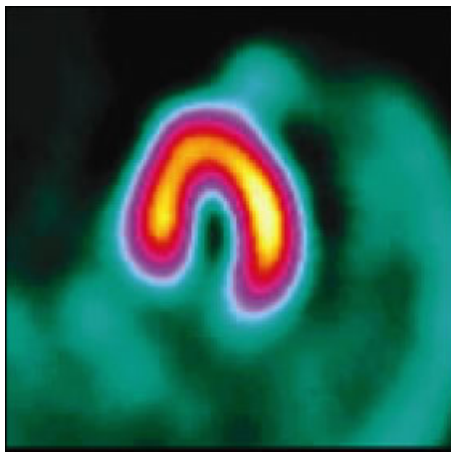
\*Correspondence to: Geoffrey T. Woolley, GE Healthcare Limited, The Maynard Centre, Forest Farm, Whitechurch, Cardiff CF14 7 YT, UK. E-mail: geoff.woolley@ge.com

<sup>†</sup>Proceedings of the Ninth International Symposium on the Synthesis and Applications of Isotopically Labelled Compounds, Edinburgh, 16–20 July 2006.

carbonate. This lyophilized powder is sealed under nitrogen and when sterile, pyrogen free sodium pertechnetate Tc-99m in saline is added to the vial, a Tc-99m complex of tetrofosmin is formed.<sup>1</sup>

### <sup>14</sup>C-ligand Radiosynthesis

The starting material for [bisphosphinoethane-1,2-<sup>14</sup>C]tetrofosmin (**4**) ligand was bis(2-ethoxyethyl)benzylphosphine (**1**)

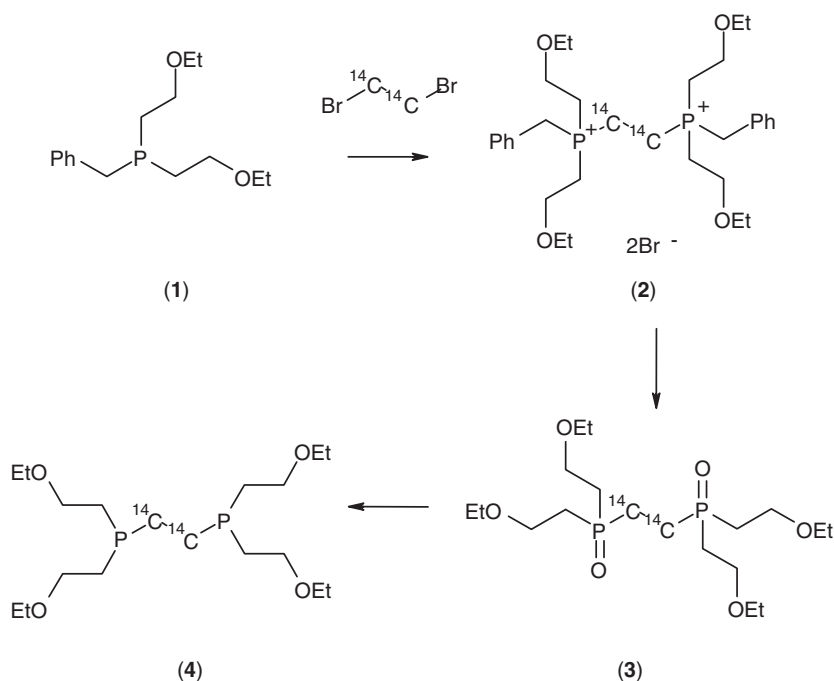


**Figure 1** Tomography image of a normal heart using Myoview™. The agent localizes in myocardial muscle, and areas of impaired activity appear as gaps in the horseshoe shape. Figure available in colour online at [www.interscience.wiley.com](http://www.interscience.wiley.com)

(**1**) (Scheme 1). This was readily prepared from diethyl benzylphosphonate [PhCH<sub>2</sub>P(O)(OEt)<sub>2</sub>] by reduction with lithium aluminium hydride to give the intermediate benzylphosphine [PhCH<sub>2</sub>PH<sub>2</sub>] in 80% yield. Then on subsequent photolysis in the presence of ethyl vinyl ether gave bis(2-ethoxyethyl) benzylphosphine (**1**) in 80% yield.<sup>5</sup> The substrate bis(2-ethoxyethyl)benzylphosphine (**1**) was heated at reflux in acetonitrile with 1,2-dibromo[U-<sup>14</sup>C]ethane (100 mCi, 20mCi/mmol) to afford [<sup>14</sup>C]compound(**2**) (97mCi). This salt was taken up in ethanol and treated with 30% aqueous sodium hydroxide. After stirring at ambient temperature and the removal of solvent the resulting residue was treated with excess concentrated hydrochloric acid. Aqueous work up gave [<sup>14</sup>C]compound (**3**) (80 mCi). [<sup>14</sup>C]Compound (**3**) (44 mCi) in dry benzene was treated with hexachlorodisilane and the resultant mixture was heated at reflux for 30 minutes then cooled. The mixture was hydrolysed with excess 30% aqueous sodium hydroxide and on aqueous work up followed by silica flash column chromatography gave the ligand [bisphosphinoethane-1,2-<sup>14</sup>C]tetrofosmin (**4**) (25mCi) which was radiochemically pure and satisfied our quality control requirements.

### Conclusion

[bisphosphinoethane-1,2-<sup>14</sup>C]Tetrofosmin (**4**) was successfully prepared in 45% overall yield from 1,2-dibromo[U-<sup>14</sup>C]ethane. This material was used to demonstrate



**Scheme 1** Radiosynthesis of [bisphosphinoethane-1,2-<sup>14</sup>C]tetrofosmin (**4**).

the safety profile of tetrofosmin. This radiosynthesis helped Myoview™ obtain marketing approval from the regulatory authorities and subsequently became one of the main heart imaging agents used today.

## REFERENCES

1. Ge Healthcare Bio-sciences. <http://www.myoview.com> print [20 August 2006].
2. The neighbourhood newsletter from GE Healthcare, April 2000.
3. Bonow RO, Dilsizian V. *J Nucl Med* 1992; **33**: 815–817.
4. Higley B, Smith FW, Smith T, Gemmell HG, Gupta PD, Gvozdanovic DV, Graham D, Hinge D, Davidson J, Lahiri A. *J Nucl Med* 1993; **34**: 30–38.
5. Chadwell SJ, Coles SJ, Edwards PG, Hursthouse MB, Imran A. *Polyhedron* 1995; **14**: 1057–1065.
6. Myoview™ kit for the preparation of Technetium Tc-99m Tetrofosmin for injection. <http://www.amershamhealthus.com/shared/pdfs/pi/Myoview.pdf> [20 August 2006].
7. Münch G, Neverve J, Matsunari I, Schröter G, Schwaiger M. *J Nucl Med* 1997; **38**: 428–432.
8. Jain D. *Semin Nucl Med* 1999; **29**: 221–236.