Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 818–830.
Published online in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1418

JLCR

Review Article

1,4-Dihydropyridines (DHPs) – a class of very potent drugs: syntheses of isotopically labeled DHP derivatives during the last four decades†

U. PLEISS*

Drug Metabolism and Isotope Chemistry, Global Drug Discovery, Bayer HealthCare AG, 42096 Wuppertal, Germany

Received 21 December 2006; Accepted 8 June 2007

Abstract: 1,4-Dihydropyridines (DHPs) belonging to the group of calcium antagonists or calcium channel blockers' are among the most important drugs used in the treatment of cardiovascular diseases. During the development processes all candidates on the market have to be labeled with isotopes. Since the discovery of 1,4-dihydropyridines (DHP) as cardiovascular drugs, the published syntheses for the labeling with radioactive isotopes like tritium, carbon-11, carbon-14, iodine-125 and stable isotopes like deuterium and carbon-13 are reviewed in the present report. The different synthetic routes are depicted and the synthesis details will be discussed with respect to the yields referred to labeled starting materials, specific activities and labeling degrees. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: dihydropyridine; calcium antagonist; deuterium; tritium; carbon-11; carbon-13; carbon-14; iodine-125

Introduction

1,4-Dihydropyridines of the general structure **1** (Figure 1) have been important and highly effective drugs for the treatment of cardiovascular diseases since nifedipine (Adalat®), the first representative of this class appeared on the market in 1975. In 2005, the total world market volume of 1,4-dihydropyridines in the world comprised 9.7 billion Euro.

The synthesis of 1,4-dihydropyridines from acetoacetic acid esters, aldehyde and ammonia was first published by A. Hantzsch in 1882.[1] Since then this procedure has proved to be highly versatile showing a considerable structural variation in the aldehydic compounds as well as in the 1,3-dicarbonyl compounds.

About 60 years later, compounds of this class were found to exhibit pharmacological activities. The 4-quinoline-substituted 1,4 dihydropyridines (Figure 2) showed considerable analgesic, morphine agonistic and spasmolytic properties, as described in a Wellcome patent in 1943.[2]

Twenty years later, extensive investigations on cardioactive compounds resulted in the development of more effective and more soluble substances by F. Bossert and W. Vater at Bayer AG. They obtained 1,4-dihydropyridines of the Hantzsch type **1** bearing substituted phenyl rings at position 4 of the dihydropyridine system,[3] which exhibited outstanding coronary vasodilator activities.[4] The 2-nitrophenyl derivative was selected as the most promising candidate for the development.[5] It was successfully introduced in Germany as nifedipine (Adalat®) in early 1975.[5] Related derivatives with antihypertensive properties were independently found by Loeve *et al.* at Smith, Kline and French.[6]

Shortly after the discovery of the cardiovascular properties of 1,4-dihydropyridines it was found that this class of substances acts by inhibiting the entry of Ca^{2+} ions into the cells of cardiac and vascular muscles through the voltage-dependent calcium channels.[7] Based on this knowledge, many dihydropyridine derivatives were synthesized worldwide in the following years. In the last four decades, numerous well-known commercial products of the second generation entered

*Correspondence to: U. Pleiss, Drug Metabolism and Isotope Chemistry, Global Drug Discovery, Bayer HealthCare AG, 42096 Wuppertal, Germany. E-mail: ulrich.pleiss@bayerhealthcare.com
†50th Anniversary Special Issue, In memoriam John Jones.

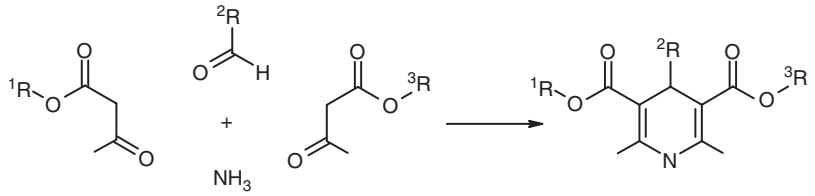


Figure 1 General synthesis of 1,4-dihydropyridines.

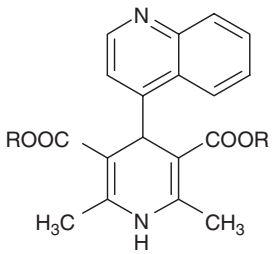


Figure 2 General DHP structure Wellcome Patent from 1943.

the market such as nimodipine,[8] nisoldipine,[9] nitrendipine,[10] amlodipine,[11] felodipine,[12] isradipine,[13] manidipine,[14] nicardipine,[15] and nilvadipine.[16] Even nowadays 1,4-dihydropyridines play a very important role as calcium antagonists as the actual analysis of the cardiovascular market shows.

During the development processes, dihydropyridines labeled with tritium[17–26] and carbon-14[27–36] proved to be indispensable in order to elucidate the mode of action and to study pharmacokinetics and drug metabolism. Special questions regarding the affinity and binding to receptor sites in various tissues were solved by utilization of dihydropyridines labeled with iodine-125.[20,37] The non-invasive imaging and quantification of dihydropyridines in living tissues by positron-emission tomography (PET) required the synthesis of carbon-11-labeled compounds.[38–44] Stable labeled dihydropyridines[45–47] were used for metabolic studies as well as internal standards for the determination in biological samples by mass spectrometry.

The present report reviews all synthetic pathways for isotopically labeled 1,4-dihydropyridines published in the literature during the last four decades.

Syntheses of tritium-labeled 1,4-dihydropyridines

In the early eighties many research groups were engaged in finding the binding sites of 1,4-dihydropyridines in cardiac and smooth muscle cells and in the brain of different animals such as rats, rabbits, guinea pigs, and canines.[17–20] For these experiments, tritium-labeled compounds were indispensable. Nitrendipine and nimodipine were the first to be labeled with tritium in the ester functions at New England Nuclear in Boston showing high specific activities.[17,19,48] Unfortunately, the exact labeling conditions were not published (Figure 3).

Holck *et al.* introduced tritium into nifedipine by dehalogenation of bromonifedipine[18] (Figure 4). The [^{3}H]nifedipine was used to determine the specific binding to rabbit heart membranes. Again no experimental details were given.

Several years later Soldatov[20] reported on tritium-labeling syntheses of the nicardipine-related 1,4-dihydropyridines **3**, **4** and **5** (Figure 5). For this purpose, *N*-benzylidenemethylamine was reduced with sodium boro[^{3}H]hydride. The resulting *N*-[^{3}H]benzyl-*N*-methylamine was reacted with a dihydropyridine bromoethylester **2** to give the final compound **3**. The specific activity was relatively low due to the addition of 8 Ci/mmol of the sodium boro[^{3}H]hydride. For photoaffinity labeling experiments on membranes of rabbit skeletal muscles, two tritium-labeled azido-dihydropyridines (**4**, **5**) were synthesized.[20] The tritium was introduced by catalytic dehalogenation of 5-iodoanthranilic acid and 3,5-diiodo-4-aminobenzoic acid, respectively, providing specific activities of 27 and 58 Ci/mmol. Conversion of the amino into azido functions was accomplished by nitrosation followed by replacement of the diazonium groups by Sandmeyer reaction. The resulting azido[^{3}H]benzoic acids were bound to the free hydroxyl group of the dihydropyridine moiety by using ethyl chloroformate and triethylamine as coupling reagent.

A related route for the labeling of ester groups in dihydropyridines with tritium was developed by Taki *et al.*[24] for [^{3}H]diazepine. Diazepine is a dihydropyridine containing a diazirine function which is suitable for locating or identifying the DHP binding sites of the ligands on the receptor molecules when it is labeled with tritium.[24] [1-^{3}H]Ethan-1-ol-2-amine was reacted with 4-(1-azi-2,2,2-trifluoromethyl)benzoic acid *N*-hydroxy-succinimide ester to give the respective [^{3}H]ethanolamide derivative (**6**). Subsequent esterification of **6** with 2,6-dimethyl-4-(2-trifluoromethyl)phenyl-1,4-dihydropyridine-3,5-dicarboxylic acid monoethyl ester

DOI: 10.1002.jlcr

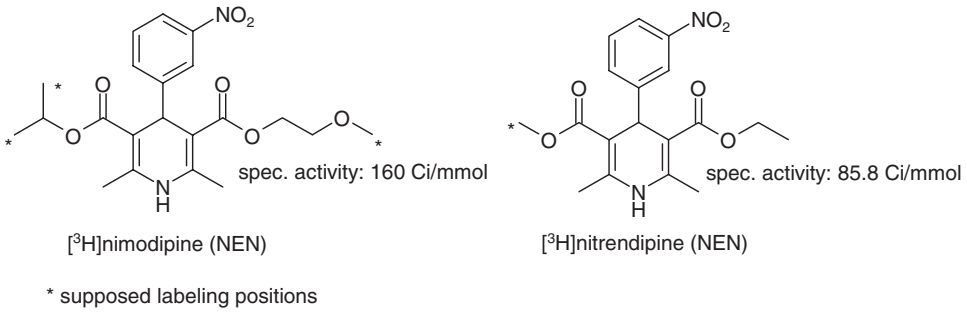


Figure 3 First tritium-labeled dihydropyridines.

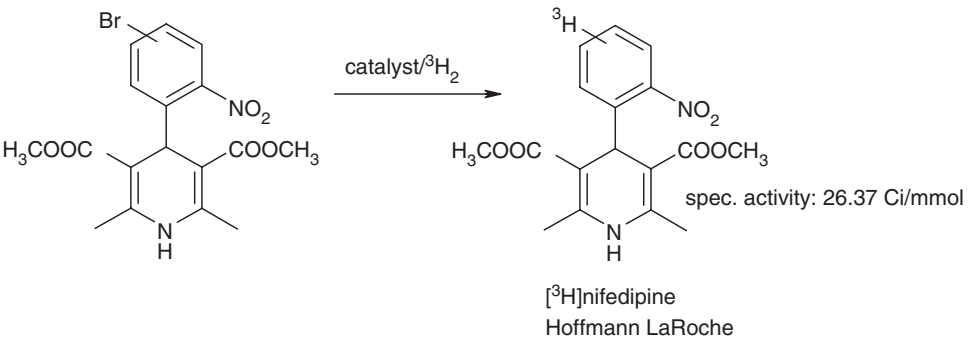


Figure 4 Tritium labeling of nifedipine.

(**7**) led to [^{3}H]diazepine with an overall yield of 40% (Figure 6).

Wu and Wang[25] reported the tritium labeling of nitrendipine in one of its ester functions starting from [^{3}H]methanol. Reaction with diketene followed by treatment of the resulting [^{3}H]methyl acetoacetate (**8**) with ammonia provided [^{3}H]methyl aminocrotonate (**9**). Refluxing of compound **9** and methyl 2-[(3-nitrophenyl)methylene]-3-oxobutanolate (**10**) afforded [5-methyl-^{3}H]nitrendipine (Figure 7). The specific activity, which depended on the starting activity of the [^{3}H]methanol employed, was 23 Ci/mmol. This multistep synthesis was carried out in about one millimolar scale, which means that a huge amount of over 20 Ci [^{3}H]methanol was used as starting material.

A direct labeling of the ester side chain was published by Shevchenko *et al.*[21] in 1989. Two analogues of riodipine (**11** and **12**) (riodipine is the symmetric 3,5-dimethylester bearing the same *o*-difluoromethoxyphenyl substituent) could be directly labeled by catalytic hydrogenation of unsaturated precursors with tritium gas (Figure 8) to afford compounds **11** and **12** with almost theoretical specific activities.

For the synthesis of [^{3}H]nicardipine, labeled in the nitrophenyl ring, Parnes and Huang[22] (Figure 9) had to carry out a multistep procedure. 2,4-Dibromo-5-hydroxymethylaniline, prepared by bromination of 3-hydroxymethylaniline, was reduced with 10 Ci tritium gas over 10% Pd/C in ethyl acetate in the presence of triethylamine. The tritiated hydroxymethylaniline was oxidized with *m*-chloroperbenzoic acid to give the respective nitro compound which was further oxidized using *m*-iodoxybenzoic acid and catalytic amounts of diphenyldiselenide to afford 3-nitro[4,6-^{3}H$_2$]benzaldehyde, the key requisite intermediate. The following reaction with methyl aminocrotonate and the appropriate acetoacetate gave [4,6-^{3}H]nicardipine with an overall yield of about 4%. The specific activity was determined to be 51 Ci/mmol.

It is always desirable to introduce tritium into the final compound by a one-step synthesis because it saves time and radioactivity as well. Therefore, Pleiss *et al.* investigated the selective catalytic dehalogenation of bromonimodipine (Figure 10) in the presence of a nitro function.[23] Palladium hydroxide on charcoal (20% Pd) proved to be the only catalyst to facilitate the selective debromination without affecting the nitro group. Other catalysts such as palladium on charcoal (10% Pd), palladium on calcium carbonate (10% Pd), palladium oxide and tris(triphenylphosphine)-palladium(II) chloride attacked preferentially the nitro group.

Experiments to achieve higher specific activities by dehalogenation of double halogenated dihydropyridines are shown by the examples of BAY w 9798 and BAY y 5959 (Figure 11).[26] As the dehalogenation of a dihalogenated precursor proceeds subsequently in two distinct reaction steps the introduction of tritium depends firstly on the extent of isotope exchange

DOI: 10.1002.jlcr

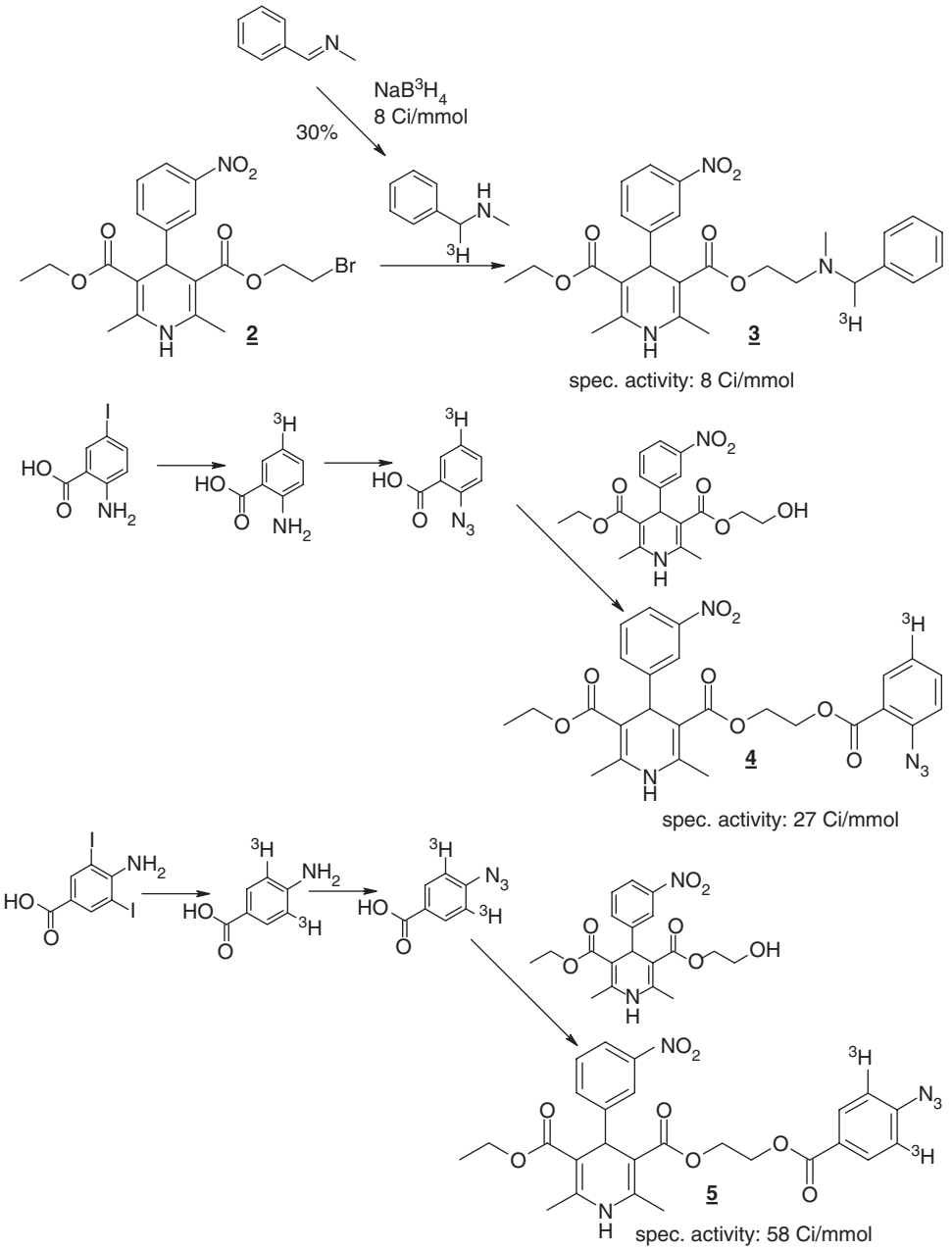


Figure 5 Tritium labeling of nicardipine-related DHPs.

between the tritium on the surface of the catalyst and the exchangeable hydrogen of the solvent and secondly on the kinetic isotope effect of the second reaction step.[26] In the case of BAY w 9798 and BAY y 5959, both effects were high and no tritium (BAY w 9798) or less tritium (BAY y 5959) was incorporated during the second dehalogenation step. Consequently, mixtures of mono-labeled and less non- and di-labeled compounds were formed with a relatively low specific activity (Figure 11).

Syntheses of carbon-14-labeled 1,4-dihydropyridines

The synthesis of [^{14}C]nifedipine, the first 1,4-dihydropyridine derivative labeled with carbon-14, was published in 1972 (Figure 12).[27] Methyl [3-^{14}C]acetoacetate was selected as an appropriate starting material, which was prepared in a six-step synthesis sequence from barium [^{14}C]carbonate. Reaction with 2-nitrobenzaldehyde and ammonia following classical Hantzsch

DOI: 10.1002.jlcr

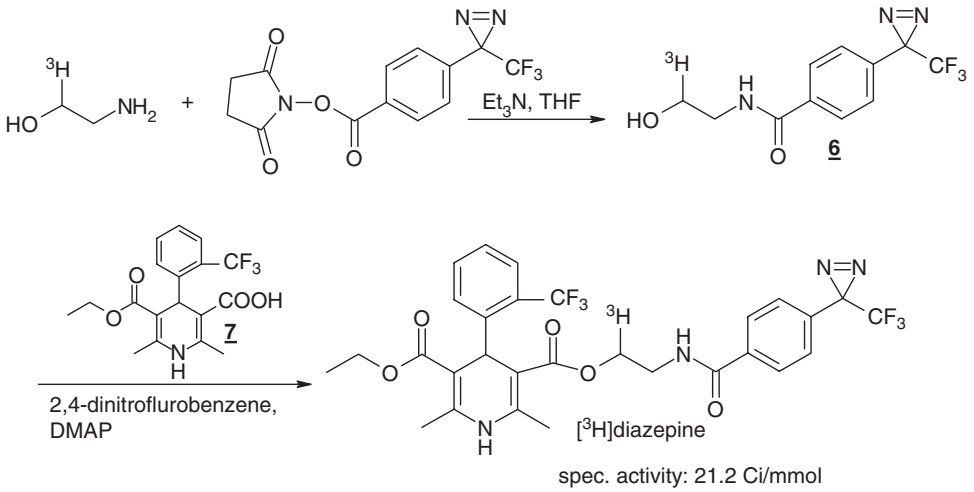


Figure 6 Synthesis of [^{3}H]diazepine.

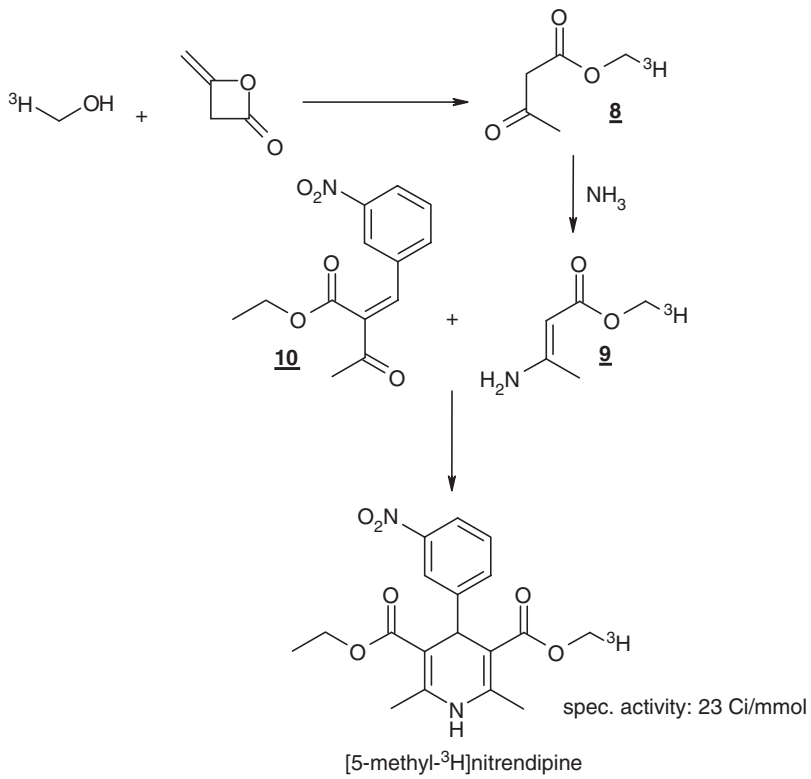


Figure 7 Synthesis of [^{3}H]nitrendipine.

conditions afforded the drug substance labeled at positions 2 and 6 with an overall radiochemical yield of 15% referred to barium [^{14}C]carbonate.

Most of the carbon-14 labeling syntheses of 1,4-dihydropyridines were started from labeled 3-amino[^{14}C]crotonic acid esters (**14**) which were prepared from the appropriate [^{14}C]acetoacetate (**13**) and ammonia in yields of about 80% following the scheme shown in Figure 13.[29–31,34–36] In many cases, the [^{14}C]acetoacetate (**13**) was synthesized by acetylation of Meldrum's acid (2,2-dimethyl-4,6-dioxo-1,3-dioxane) and subsequent alkoholysis in yields of about 50–75%.[34–36] Wilkinson[33] slightly modified the two ways depicted in Figure 13 by using [5-^{14}C]Meldrum's acid as an

DOI: 10.1002.jlcr

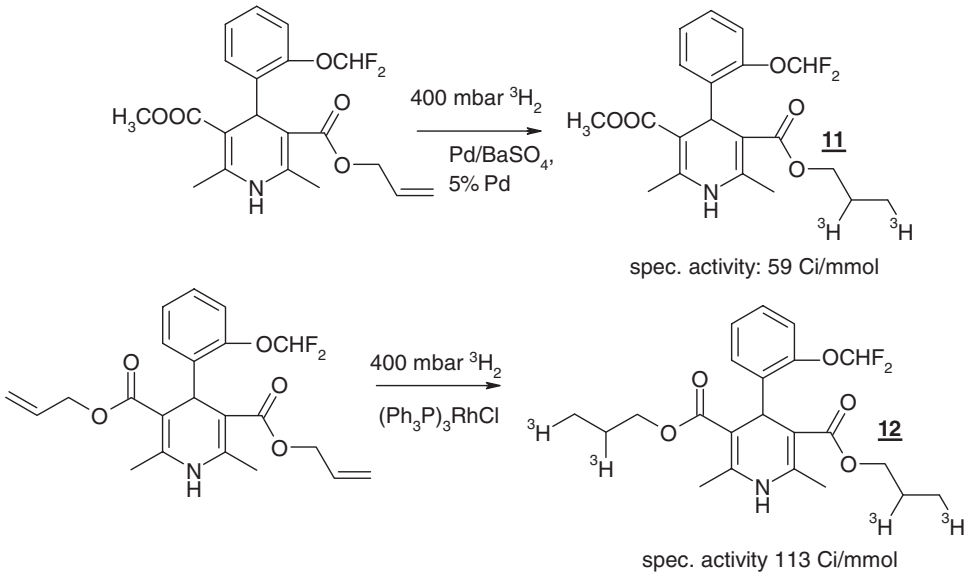


Figure 8 Tritium labeling of riodipine analogues.

appropriate precursor, which was readily obtained by acid catalyzed reaction of [2-^{14}C]malonic acid and acetone. In principle, the known cyclizing Michael addition using 3-aminocrotonates (**14**) and substituted 2-benzyliden-acetoacetates (**16**) (two-component reaction) or 3-aminocrotonate **14**, benzaldehydes (**15**) and acetoacetates **13** (3-component reaction) was used for all carbon-14 labeling syntheses of 1,4-dihydropyridines (**17**) ever published in the literature (Figure 13). Depending on the desired labeling positions in the DHPs different labeled acetoacetates or aminocrotonates were used as starting materials. Applying these synthetic pathways, dihydropyridines were labeled in positions 2,[29,36] 5,[33] 6,[30,31,34] 5-carboxy and 6.[35] The yields for the cyclization reactions were in the range of about 40–70%.

[Carbonyl-^{14}C]benzaldehydes were selected as alternative starting materials for the syntheses of 1,4-dihydropyridines labeled at position 4.[28,32,34] Walkenstein *et al.*,[28] for example, synthesized 2-trifluoromethyl[carbonyl-^{14}C]benzaldehyde in two steps by cyano-halogen exchange of an iodo-precursor with Cu^{14}CN and diisobutylaluminum hydride (DIBAH) reduction yielding the desired [^{14}C]aldehyde (Figure 14) which was used for the synthesis of a symmetric 3,5-diethylester. In a similar manner, Parnes *et al.*[32] carbonated bromobenzene with $^{14}CO_2$ to obtain [^{14}C]benzoic acid which was esterified with methanol, nitrated by nitric acid and subsequently reduced with DIBAH. The reduction could not be controlled to give the desired aldehyde without over-reduction to the benzyl alcohol. This mixture was, therefore, oxidized using catalytic diphenyldiselenide and *m*-iodoxybenzoic acid in refluxing toluene (Figure 14). Further reaction with nicardipine and RS-93552 was carried out by a three-component reaction as shown in Figure 13. Scherling and Pleiss[34] succeeded in preparing 2-nitro[carbonyl-^{14}C]benzaldehyde in a two-step one pot sequence by Br/Li-replacement of 2-bromo-1-nitrobenzene with phenyllithium at -100°C followed by formylation of the aryllithium formed with dimethyl [^{14}C]formamide.

All carbon-14-labeled 1,4-dihydropyridines published so far are depicted in a chronological sequence in Figure 15. Although those bearing different ester functions represent chiral compounds, only [^{14}C]YM-09730-5 (Figure 15) was made available in enantiomerically pure form. Single enantiomers may differ in their pharmacological effects and even exhibit opposite activities by acting as agonists or antagonists.[49] However, all chiral 1,4-dihydropyridines presently on the market were developed as racemates.

Syntheses of carbon-11-labeled 1,4-dihydropyridines

For investigations into the *in vivo* function of calcium channels, 1,4-dihydropyridines were also labeled with carbon-11.[38–44] Due to the short half-life and the very short synthesis time (30–60 min after bombardment) all examples so far published for the carbon-11 labeling of 1,4-dihydropyridines follow a common synthetic principle: ^{11}C-introduction in one of the ester groups. The syntheses differ

DOI: 10.1002.jlcr

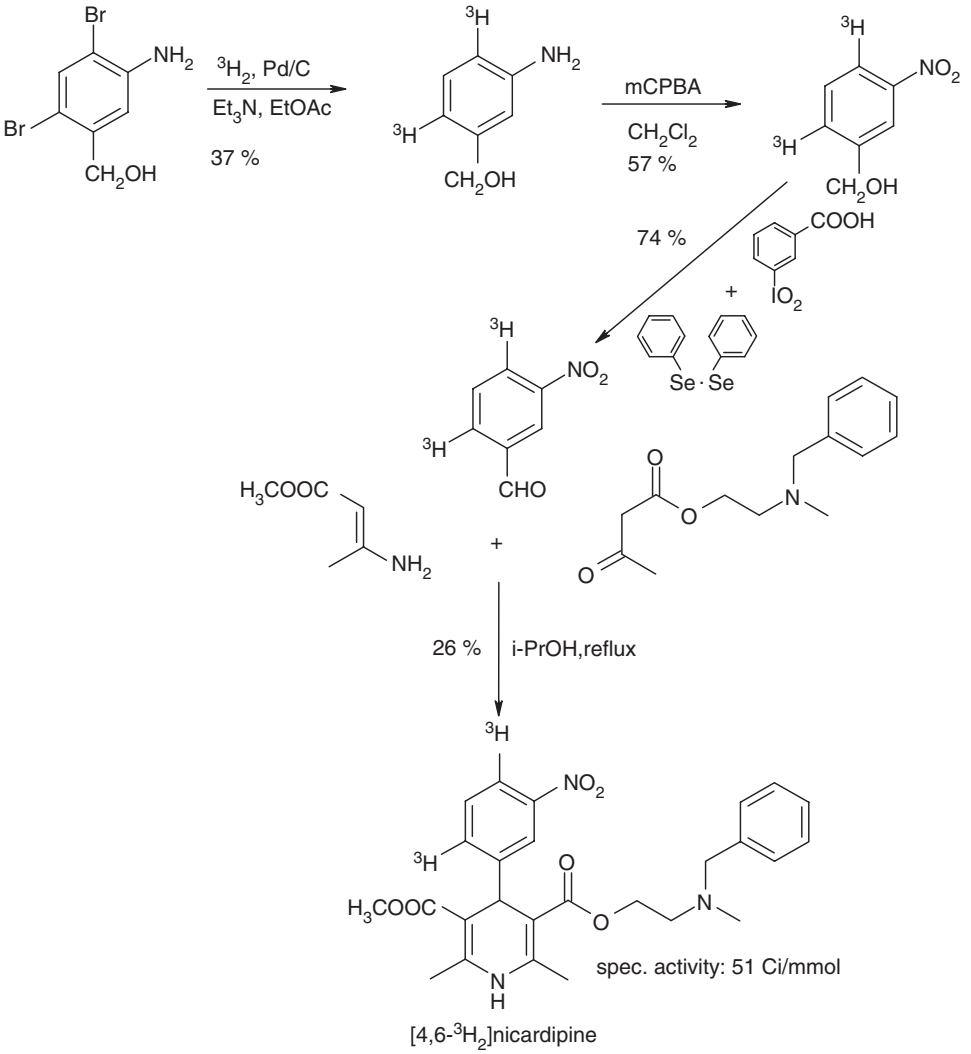


Figure 9 Tritium labeling of nicardipine.

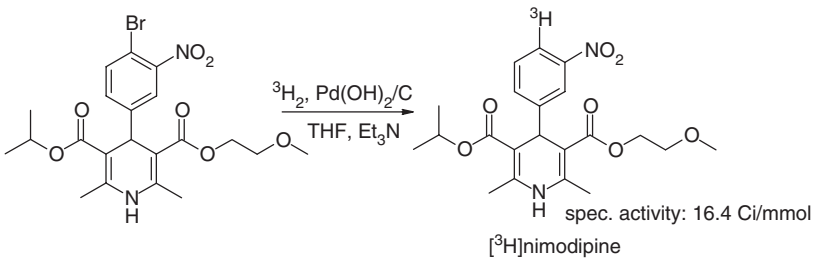


Figure 10 Synthesis of [^{3}H]nimodipine.

only in the preparation of the labeled alcoholic component and the conditions for the ester formation (Figure 16).

The labeling of nifedipine and nicardipine was accomplished by one-step esterification of the appropriate monocarboxylic acid precursors using [^{11}C]iodomethane in the presence of tetrabutylammonium hydroxide in DMF.[38] Holschbach *et al.*[41] also selected [^{11}C]iodomethane as the most appropriate starting material for the synthesis of [^{11}C]nifedipine, [^{11}C]nisoldipine, [^{11}C]nitrendipine and CF_3-[^{11}C]nifedipine

DOI: 10.1002.jlcr

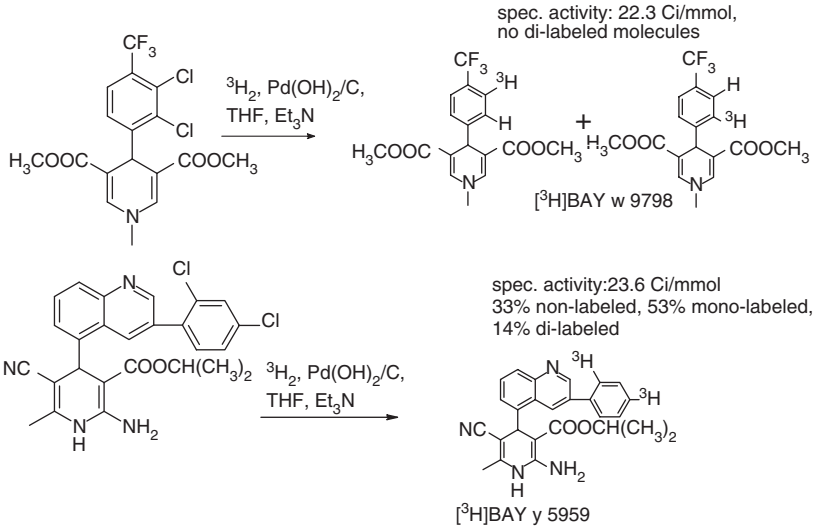


Figure 11 Dehalogenation of dichlorinated precursors.

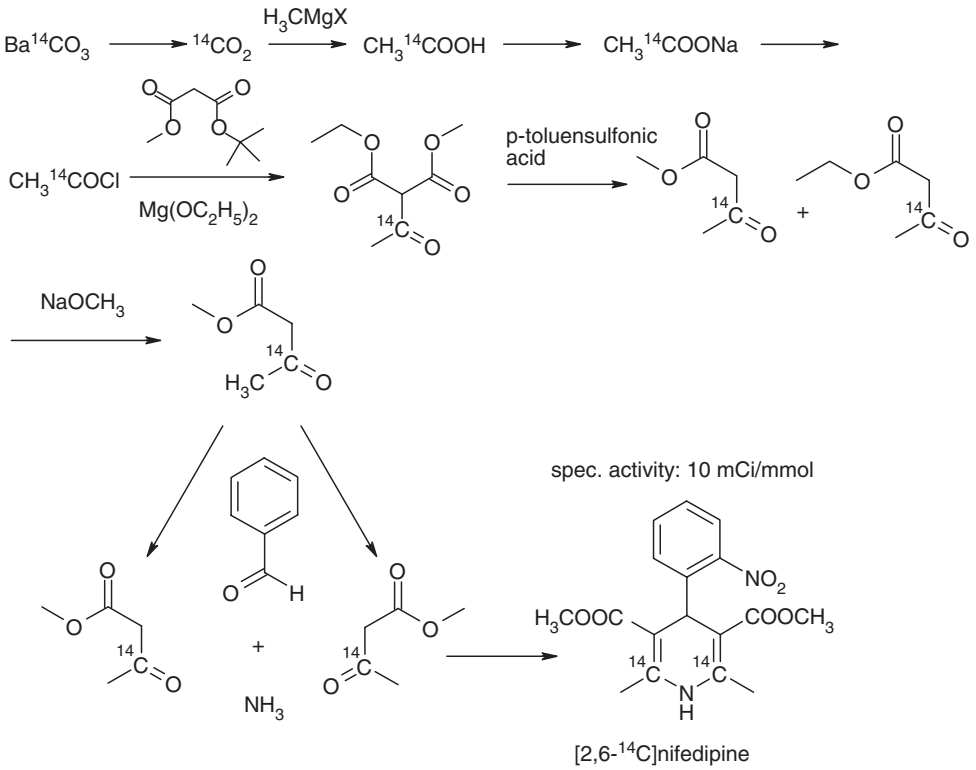


Figure 12 Synthesis of [^{14}C]nifedipine.

(CF_3 group instead of nitro), but in all cases coupling to the potassium salts of the dihydropyridine monocarboxylic acids was carried out under phase transfer conditions (*cis*-dicyclohexano-18-crown-6 as catalyst). For the labeling of nimodipine [2-^{11}C]isopropyl iodide was prepared by reaction of $^{11}CO_2$ and methyl lithium (2 equivalents), $LiAlH_4$ reduction and reaction of the resulting [2-^{11}C]isopropanol with hydriodic acid.[39,43] Esterification of desisopropyl nimodipine was accomplished using potassium carbonate and 2,2,6,6-tetramethylpiperidine as bases. Coenen *et al.*[42] and Holschbach *et al.*[44] reported the C-11 labeling of nimodipine in the opposite ester function. [^{11}C]Methoxyethanol, needed as the labeled key intermediate,

DOI: 10.1002.jlcr

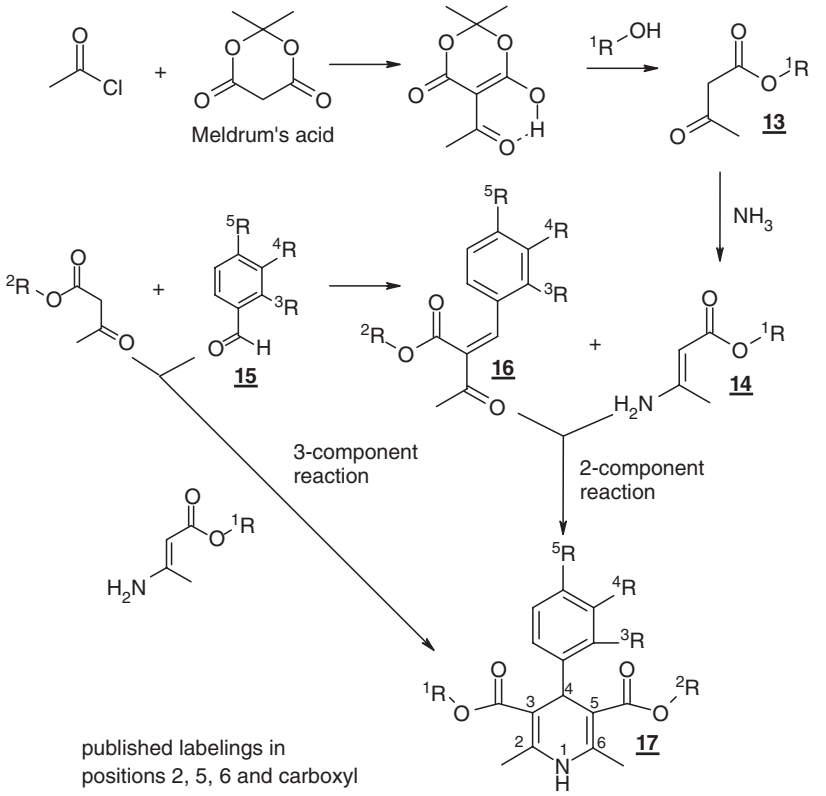


Figure 13 General synthetic pathways for ^{14}C-labeling of 4-aryl-1,4-dihydropyridines.

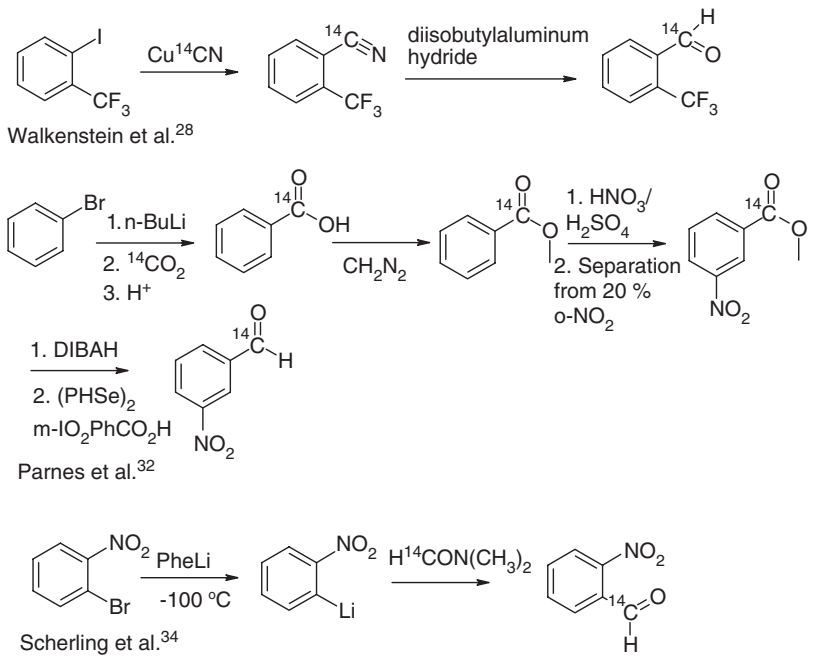


Figure 14 Synthetic pathways to carbon-14-labeled benzaldehydes.

was prepared by reaction of mono-deprotonated glycol with [^{11}C]methyl iodide in acetonitrile in the presence of 18-crown-6 as phase transfer catalyst. It was coupled to the free carboxyl group following carbonyldiimidazol[42] or acid chloride methodology[44] in the presence of an appropriate base.

DOI: 10.1002.jlcr

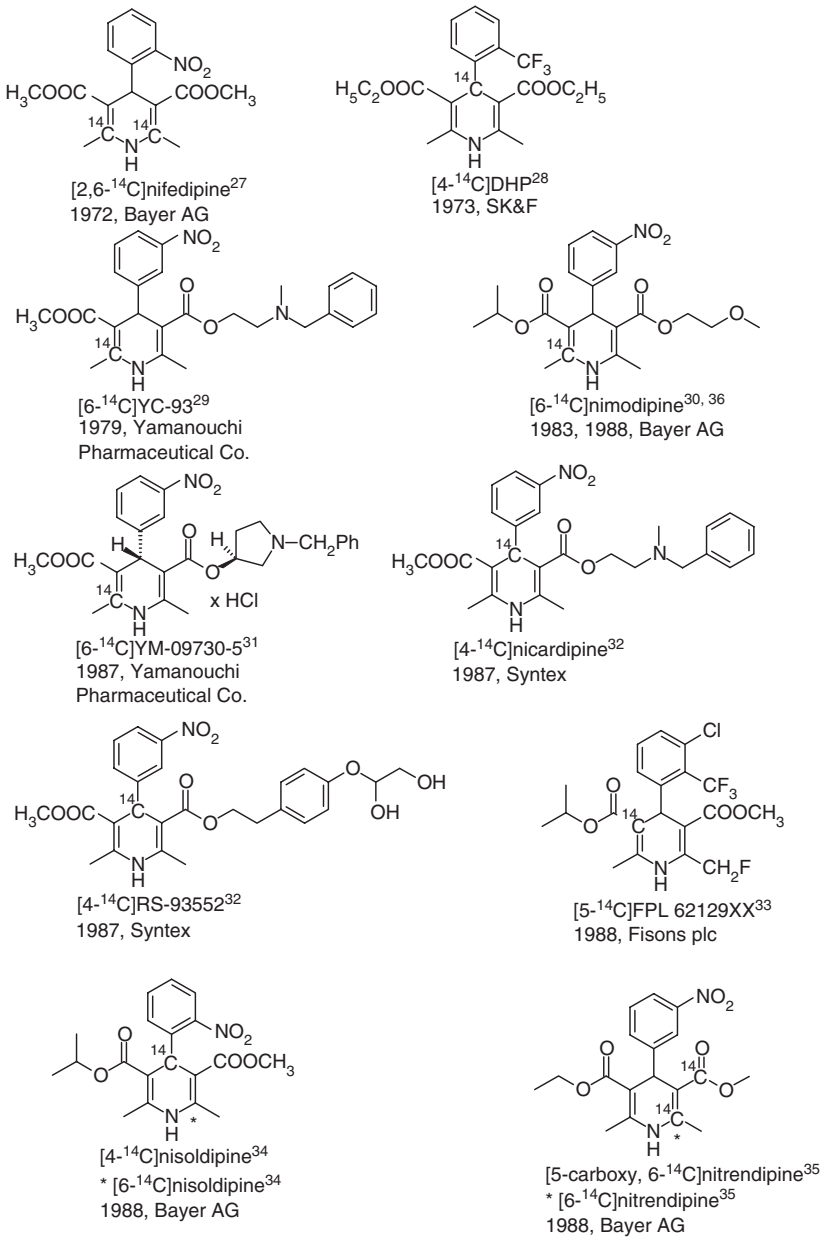


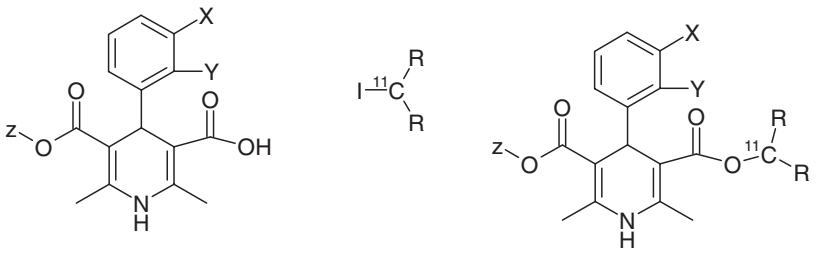
Figure 15 Published carbon-14-labeled dihydropyridines.

Isradipine, an 3-isopropyl-5-methylester 1,4-dihydropyridine derivative, was labeled by esterification of the corresponding monocarboxylic acid with [^{11}C]diazomethane. The latter was prepared from [^{11}C]methane, followed by chlorination to [^{11}C]chloroform and reaction with hydrated hydrazine.[40]

Labeling of 1,4-dihydropyridines with stable isotopes

Nowadays pharmaceutical development candidates are often labeled with stable isotopes in order to use them as internal standards for LC–MS bioanalytical monitoring of the drug in toxicological and clinical studies. Thirty years ago, however, this method was not generally established so that only a few syntheses of 1,4-dihydropyridines labeled with stable isotopes were published.[45–47] For investigations into primary and secondary deuterium isotope effects in metabolism reactions multiple deuterated nifedipine was synthesized by Rampe *et al.*[45] Methyl acetoacetate was refluxed with a large excess of d_4-methanol and a catalytic amount of sodium d_3-methoxide to produce [$^2H_3$]methyl [$^2H_5$]acetoacetate, which showed

DOI: 10.1002.jlcr



nifedipine[37,40]: X=H, Y=NO_2, Z=CH_3, R=H
nicardipine[37]: X=NO_2, Y=H, Z=$CH_2CH_2N(CH_3)CH_2Phe$, R=H
nimodipine[38,42]: X=NO_2, Y=H, Z=$CH_2CH_2OCH_3$, R=CH_3
nisoldipine[40]: X=H, Y=NO_2, Z=$CH_2CH(CH_3)_2$, R=H
nitrendipine[40]: X=NO_2, Y=H, Z=CH_2CH_3, R=H
CF_3-nifedipine[40]: X=H, Y=CF_3, Z=CH_3, R=H

Nimodipine was also labeled by monomethylation of glycol using [^{11}C]methyl iodide and following esterification[41,42].

Figure 16 General synthetic pathways to [^{11}C]dihydropyridines.

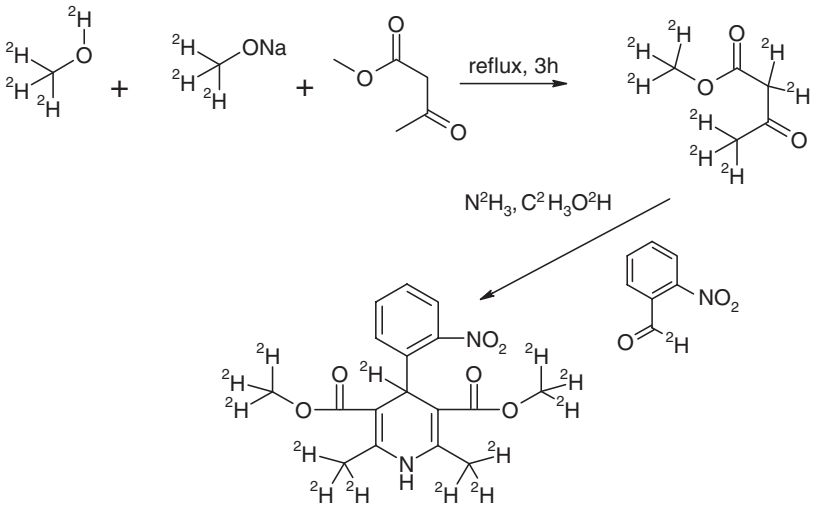


Figure 17 Synthesis of multiple deuterated nifedipine.

an isotopic purity of 90%. The following Hantzsch condensation with 2-nitro-[^{2}H]benzaldehyde, perdeuterated ammonia and methanol led to [$^2H_{13}$]nifedipine with 59% yield (Figure 17).

Ohtaka and Kajiwara[47] used the reaction sequence shown in Figure 7 for stable isotope labeling of nifedipine. Starting from [^{13}C]methanol esterification with diketene in the presence of a catalytic amount of dry triethylamine afforded [^{13}C]methyl acetoacetate. Reaction of this product with 2-nitrobenzaldehyde and ammonia yielded [$^{13}C_2$]nifedipine.

For the preparation of deuterated nilvadipine[46] as the internal standard for LC–MSMS analytics, the respective monocarboxylic acid dihydropyridine was esterified with [$^2H_4$]methanol (Figure 18) similar to the procedures known from the carbon-11 synthesis. The methyl ester of nilvadipine was selectively cleaved using lithium iodide in refluxed pyridine. The resulting lithium salt was reacted with [$^2H_4$]methanol in the presence of 1-methyl-2-bromopyridinium iodide and *N*,*N*-dimethylaniline to afford [$^2H_3$]nilvadipine.

Syntheses for labeling of 1,4-dihydropyridines with other isotopes

Two examples for labeling of 1,4-dihydropyridines with iodine-125 were published in the literature[20,37] (Figure 19). In one case, a mesylate derivative was

DOI: 10.1002.jlcr

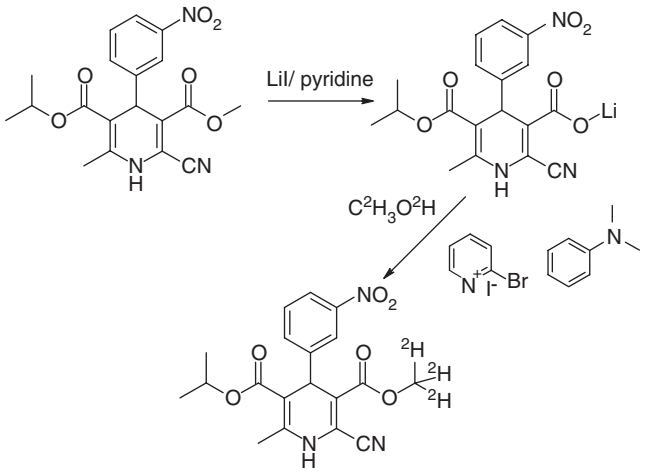


Figure 18 Synthesis of [methyl-$^{2}H_3$]nilvadipine.

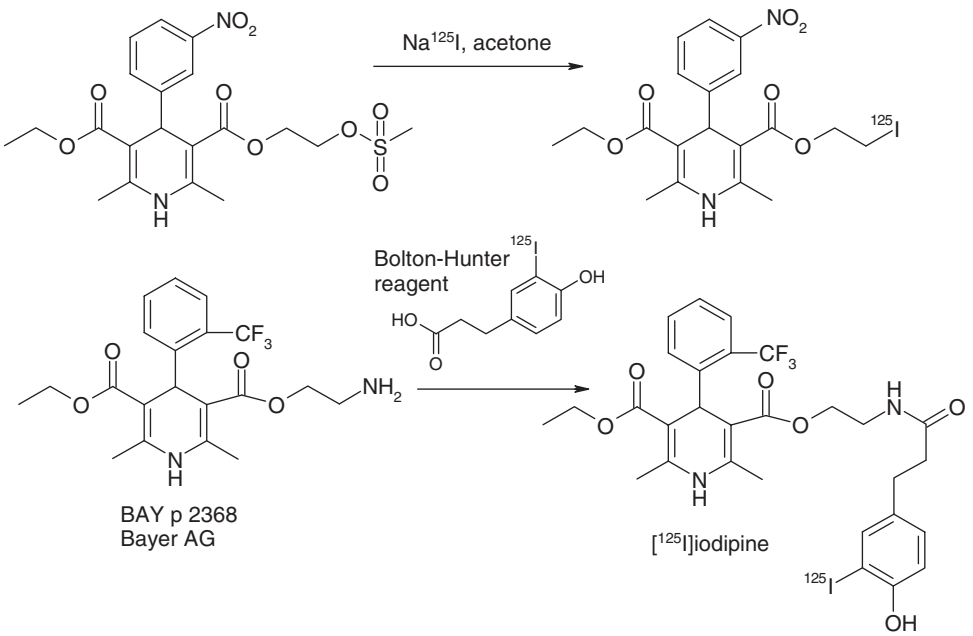


Figure 19 Labeling of 1,4-dihydropyridines with I-125.

reacted with dry sodium [^{125}I]iodide in acetone to afford a ^{125}I-labeled dihydropyridine.[20] Demmer *et al.*[37] described the labeling of Bay p 2368 with Bolton–Hunter reagent yielding 2000 Ci/mmol as specific activity.

Acknowledgement

The author thanks Dr Rolf Voges for discussions and editorial assistance.

REFERENCES

1. Hantzsch A. *Justus Liebigs Ann Chem* 1882; **215**: 1–82.
2. Phillipps AP, Randall LD. *US 2 359 329*. Wellcome, 1943.
3. Bossert F, Vater W. *Med Res Rev* 1989; **9**: 291–324.
4. Bossert F, Vater W. *DE 1 493677*. Bayer AG, 1964.
5. Bossert F, Vater W. *Naturwissenschaften* 1971; **58**: 578.
6. Love B, Tedeschi RE. *US 3 511 847*. Smith, Kline and French, 1970.
7. Fleckenstein A, Grün G. *Arzneim Forsch* 1972; **22**: 334–344.
8. Kazda R, Towart R. *Br J Pharmacol* 1981; **72**: 582–583.

9. Kazda S, Garthoff B, Meyer H, Schlossmann K, Stoepel K, Towart R, Vater W, Wehinger E. *Arzneim Forsch* 1980; **30**: 2144–2162.
10. Stoepel K, Heise A, Kazda S. *Arzneim Forsch* 1981; **31**: 2056–2064.
11. Arrowsmith JE, Campbell SF, Cross PE, Stubbs JK. *Pharmacologist* 1985; **27**: 290.
12. Nyborg NCB, Mulvany MJ. *J Cardiovasc Pharmacol* 1984; **6**: 499–505.
13. Hof RP, Scholtysik G, Loutzenhiser R, Vuorela HJ, Neumann P. *J Cardiovasc Pharmacol* 1984; **6**: 399–406.
14. Meguro K, Aizawa M, Sohda T, Kawamatsu Y, Nagaoka A. *Chem Pharm Bull* 1985; **33**: 3787–3797.
15. Takenaka T, Usuda S, Nomura T, Maeno H, Sado T. *Arzneim Forsch* 1976; **26**: 2172–2178.
16. Furuta T, Shibata S, Kodama I, Yamada K. *J Cardiovasc Pharmacol* 1983; **5**: 836–841.
17. Janis RA, Maurer SC, Sarmiento JG, Bolger GT, Triggle DJ. *Eur J Pharmacol* 1982; **82**: 191–194.
18. Holck M, Thorens S, Haeusler G. *Eur J Pharmacol* 1982; **85**: 305–315.
19. Ehlert FJ, Itoga E, Roeske ER, Yamamura HI. *Biochem Biophys Res Commun* 1982; **104**: 937–943.
20. Soldatov NM. *Bioorg Chem* 1989; **17**: 141–158.
21. Shevchenko VP, Myasoedov NF, Soldatov NM, Duburs GJ, Kastron VV, Skrastins IP. *J Label Compd Radiopharm* 1989; **27**: 721–730.
22. Parnes H, Huang GT. *J Label Compd Radiopharm* 1991; **29**: 87–93.
23. Pleiss U, Schmitt P. *J Label Compd Radiopharm* 1991; **29**: 1091–1094.
24. Taki M, Kuniyasu A, Nakayama H, Kanaoka Y. *Chem Pharm Bull* 1991; **39**: 1860–1862.
25. Wu D, Wang W. *J Label Compd Radiopharm* 1996; **39**: 105–107.
26. Pleiss U, Rosentreter U, Stoltefuss J, Behner O. In *Synthesis and Application of Isotopically Labelled Compounds 1997*, Heys JR, Melillo DG (eds). Wiley: New York, 1998; 207–211. ISBN 0-471-97863-9.
27. Duhm B, Maul W, Medenwald H, Patzschke K, Wegner LA. *Arzneim Forsch* 1972; **22**: 42–43.
28. Walkenstein SS, Intoccia AP, Flanagan TL, Hwang B, Flint D, Weinstock J, Villani AJ, Blackburn D, Green H. *J Pharm Sci* 1973; **62**: 580–584.
29. Iwanami, M, Shibanuma T, Fujimoto M, Kawai R, Tamazawa K, Takenaka T, Takahashi K, Murakami M. *Chem Pharm Bull* 1979; **27**: 1426–1440.
30. Meyer H, Wehinger E, Bossert F, Scherling D. *Arzneim Forsch* 1983; **33**: 106–111.
31. Arima H, Tamazawa K, Takeuchi M. *J Label Compd Radiopharm* 1987; **25**: 161–170.
32. Parnes H, Huang GT, Shelton EJ. *J Label Compd Radiopharm* 1987; **25**: 621–626.
33. Wilkinson DJ. *Appl Radiat Isot* 1988; **39**: 554.
34. Scherling D, Pleiss U. *J Label Compd Radiopharm* 1988; **25**: 1393–1400.
35. Maul W, Scherling D. *J Label Compd Radiopharm* 1988; **26**: 457–463.
36. Scherling D. *J Label Compd Radiopharm* 1989, **27**: 599–603.
37. Demmer A, Andreae S, Thole H, Tümmler B. *Eur J Biochem* 1999; **264**: 800–805.
38. Wilson AA, Dannals RF, Ravert HT, Burns HD, Lever SZ, Wagner HN. *J Label Compd Radiopharm* 1987; **27**: 589–598.
39. Stone-Elander S, Roland P, Halldin C, Schwenner E, Boeshagen H, Widen L. *J Label Compd Radiopharm* 1989; **26**: 238–239.
40. Crouzel C, Syrota A. *Appl Radiat Isot* 1990; **41**: 241–242.
41. Holschbach M, Roden W, Hamkens W. *J Label Compd Radiopharm* 1991; **29**: 432–442.
42. Coenen HH, Schueller M, Stoecklin G, Schwenner E. *J Label Compd Radiopharm* 1991; **30**: 245–247.
43. Stone-Elander S, Roland P, Schwenner E, Halldin C, Widen L. *Appl Radiat Isot* 1991; **42**: 871–875.
44. Holschbach M, Coenen HH, Schueller M, Goldmann S, Stoecklin G. *J Label Compd Radiopharm* 1993; **32**: 189–190.
45. Rampe D, Hake PW, Borretzen B, Holm KH, Skattebol L. *Eur J Med Chem* 1993; **28**: 259–263.
46. Satoh Y, Okumura K, Shiokawa Y. *Chem Pharm Bull* 1994; **42**: 950–952.
47. Ohtaka K, Kajiwara M. *J Label Compd Radiopharm* 2003; **46**: 1177–1179.
48. Murphy KMM, Snyder SH. *Eur J Pharmacol* 1982; **77**: 201–202.
49. Goldmann S, Stoltefuss J. *Angew Chem Int Ed Engl* 1991; **30**: 1559–1578.

DOI: 10.1002.jlcr