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Review Article

Isotopic methylation

R. Bolton*
Department of Chemistry, School of Physical Sciences, University of Surrey, Guildford, Surrey GU2 7XH, UK

Summary

This review reports recent methods by which organic compounds, and especially pharmaceuticals, have been isotopically labelled by the incorporation of carbon or hydrogen isotopes in methylation processes. Particular attention is paid to the incorporation of carbon-11; both the synthesis of such labelled methylating agents and applications of their use are discussed. The review has reported reagents and conditions by which a number of organic compounds have been obtained recently. It also assesses the limitations of reported methods and proposes some alternative techniques and innovations.

The application of catalysts such as Ag^+ and conditions such as microwave irradiation to encourage these reactions are also included, with suggestions of other, potentially beneficial, ways to assist them.

In many cases, the radio-chemical yield and purity of the labelled product are given along with an estimate of the total reaction time.

Key Words: methylation; carbon isotopes; hydrogen isotopes; C- and H-labelled methylating agents

Review

Available isotopes; limitations

Isotopic methylation involves the labelling of an organic compound, often a pharmaceutically active material, by changing the relative

*Correspondence to: R. Bolton, Chemistry Department, University of Surrey, Guildford, Surrey GU2 7XH, UK.

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isotopic abundance of carbon or hydrogen atoms in methyl substituents. In recent years this has often been achieved by demethylation of the material and re-alkylating it using labelled reagents, though other methods are available and have been used.

In principle, a labelled alkyl substituent may be introduced into an organic structure by any of the appropriate methods of organic chemistry. This is especially the case when the organic structure is a pharmacologically active compound whose synthesis involves such an alkylation step. Demethylation and subsequent methylation of naturally occurring organic compounds using isotopically labelled organic reagents is useful if the original compound is stable to the demethylation conditions, which are often strongly acidic. Methylation is often achieved using methyl halides; condensation of amino-functions with formaldehyde (methanal) followed by reduction of the multiple bond offers another route.

In practice, there are some constraints. The first and most obvious one is the half-life of the radioisotope which is to be introduced. Deuterium, tritium ($t_{1/2}$, 12.7 year), carbon-13 and carbon-14 ($t_{1/2}$, 5570 year) may be incorporated by any appropriate synthetic methods; lengthy purification processes, for example, are no disadvantage. The choice of the chemical method used to incorporate these isotopes into organic compounds is only conditioned by the form in which the label is available – in other words, the source of the radioisotope and the chemistry by which it is incorporated into an organic reagent. Labelling with deuterium or tritium requires that the hydrogen isotope, having been introduced to the methyl group, is stable to the reaction conditions. While hydrogen exchange in alkyl systems can be achieved, it usually requires strongly acidic, often aprotic, reaction conditions, and so loss of the inserted hydrogen isotope is generally unlikely unless such forcing conditions are present.

However, the short half-life of carbon-11 poses problems of its own. The range of chemistry available to prepare the methylating agent is now limited both by the chemical form in which the radioisotope is usually available and by the speed with which the methylating agent is destroyed by radioactive decay. As the main source of carbon-11, from bombardment in the cyclotron, is [C-11]-carbon dioxide[1] the preferred route to a methylating agent involves reduction to [C-11]-methanol or [C-11]-methane, both of which may be made quickly.[2]

Preparation and application of [C-11]-methylating agents[3]

Carbon-13 is typically obtained by proton bombardment of nitrogen, as in the attack by protons at 10 μA upon N_2/5% H_2 over 1 min. *[C-11]-methyl iodide*[4–6] may be prepared from [C-11]-carbon dioxide by reduction to [C-11]-methanol and then treatment with a source of HI. The reduction is carried out either by catalytic hydrogenation (using deuterium or tritium where necessary) or more often by lithium aluminium hydride ($LiAlH_4$). Again, isotopomers of methanol are formed if $LiAl^2H_4$ or $LiAl^3H_4$ are used. As the carbon dioxide, methanol, and methyl halide are all volatile, separation from non-volatile impurities is easily achieved by distillation or gas chromatography.

One of the earlier reports[7] of this synthesis gives commendable experimental detail for each step, together with the radio-chemical losses associated with the various purification processes. Many other descriptions[8–12] of the preparation of [C-11]-iodomethane are based upon this, although triphenylphosphite ethyl iodide has generally been replaced by aqueous HI.[13] An alumina column, treated with ethereal $LiAlH_4$, allows [C-11]-carbon dioxide in the gas stream to be directly trapped and reduced. Treatment of the resulting salts with dilute phosphoric acid provides [C-11]-methanol; both steps proceed in $>95\%$ yield. Hydrogen iodide absorbed on an alumina column has been advocated as a simple and fast reagent, giving [C-11]-methyl iodide in optimum yields of 97%.[14] The authors claim a total synthesis time of 6 min.[15] Perhaps this sequence could be made even faster if HI were used directly upon the lithium aluminium alkoxides; this has been promoted as a means of obtaining alkyl halides directly without the isolation of the intermediate alcohols.

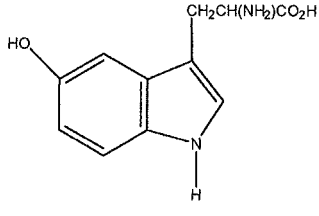
A recent and typical example of this process is the synthesis of [C-11]-methyl iodide in $31 \pm 8\%$ radio-chemical yield from EOB,[†] and in a total synthesis time of 35 min.[16] [C-11]-methyl iodide has also been prepared ($60 \pm 10\%$ radio-chemical yield) from [C-11]-methane through substitution by iodine.[17] [C-11]-*methyl bromide* also has been made from [C-11]-methane.[18] In one set of conditions, [C-11]-CO_2 was 'efficiently hydrogenated' to provide [C-11]-methane which passed through liquid bromine. The mixture of halogen and alkane was taken to a hot tube, and the resulting mono- and di-bromomethanes were

[†] End of bombardment of the cyclotron target and the formation of $^{11}CO_2$.

separated, when the [C-11]-bromomethane was taken on to a remote on-line synthesis of [C-11]-methyl triflate.[19] In another, [C-11]-methane is recirculated over pyridinium tribromide at 50°. The [C-11]-bromomethane (63–71% yield), after a single pass over silver triflate at 280°, gave [C-11]-methyl triflate in 80–90% yield; surprisingly, the yield was better than that reported from [C-11]-methyl iodide.[18]

Automated processes for the preparation of [C-11]-methyl iodide in this way have been recently described;[20] Larsen and his colleagues[21] have reported the automated on-line preparation of [C-11]-methyl iodide in 1.0 Ci quantities. [C-11]-methane and iodine in helium were recirculated through a tube at 700–750°, removing the iodomethane as it was formed. After allowance for decay, an 83% yield of [C-11]-iodomethane was obtained after 7 min. This process has been successfully applied[22] in syntheses of [16-C-11]-hexadecanoic acid (**1**; $^{11}CH_3 \cdot (CH_2)_{14} \cdot CO_2H$) by three separate routes.

The automated synthesis of [C-11]-L-aminoacids from [C-11]-carbon dioxide via [C-11]-methyl iodide allowed the preparation of [C-11]-L-5-hydroxytryptophan (**2**, 97% radio-chemical purity, 1100 ± 200 Ci mmol^{-1}) in 32 min, and of [C-11]-L-DOPA (**3**).[23]



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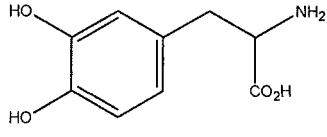

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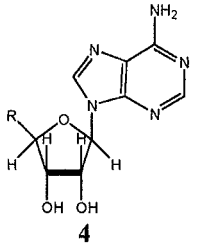
A similar apparatus allows the automated production of [C-11]-methyl iodide, which leads to enzyme-induced reactions to provide [C-11]-L-DOPA from catechol, and [C-11]-L-5-HTP (**2**) from 5-hydroxyindole in 23 and 29 min, respectively.[24] Enzyme-encouraged



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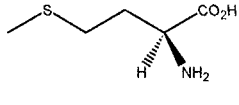

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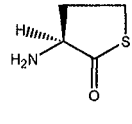

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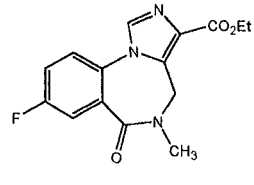

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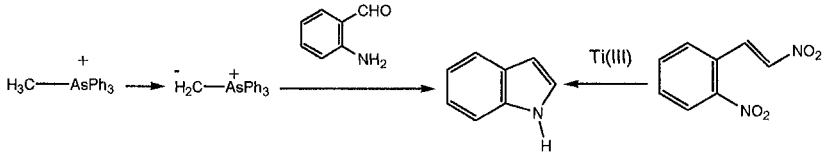
processes, such as the preparation of [C-11]-*S*-adenosyl-methionine (**4**; R = $HO_2C \cdot CH(NH_2) \cdot CH_2 \cdot CH_2 \cdot S(CH_3)^+ \cdot CH_2$–),[25] are occasionally

invaluable in the automated stereospecific synthesis of labelled pharmaceuticals and other natural products. Quality control of the routine production of [C-11]-L-methionine (**5**) has been described.[26] Another automated preparation of [C-11]-methyl iodide gave [C-11]-choline in 44% radio-chemical yield after 20 min.[27] In a variant upon these designs, [C-11]-methyl iodide and supercritical ammonia are used to achieve the *O*-[C-11]-methylation of phenol or the synthesis of ([C-11]-methyl)-L-methionine (**5**) from homocysteine thiolactone hydrochloride (**6**).[28]

Microwave irradiation substantially accelerates alkylation of neuroreceptors by [C-11]-methyl iodide or by [2-C-11]-isopropyl iodide.[29] The effect is probably general, both within the range of alkylation reactions and within organic chemistry, and it should be considered in [C-11]-labelling processes where the equivalent thermal reaction is excessively slow. Recently, [C-11]-methylation by iodomethane to give [C-11]-flumazenil (**7**) has been achieved using robotics; the formulation of the labelled drug was completed 18 min after the condensation of the [C-11]-methyl iodide. The solid-phase alkylation took place with KF as the base; the methylated drug was readily separated from its precursor.[30]

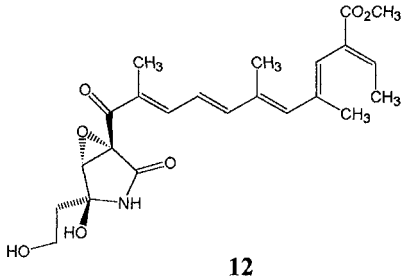
Many uses of [C-11]-methyl iodide involve nucleophilic attack, as is exemplified by the preparation of [C-11]-methyltriphenylarsonium iodide (**8**) from Ph_3As.[31]



8 **9** **10** **11**

Expectedly, BuLi gave triphenylarsonium [C-11]-methylide (**9**) from which reaction with *o*-aminobenzaldehyde provided [2-C-11]-indole (**10**) in 23–27% yield after 15 min.[32] This may also be made from [C-11]-methyl iodide through [C-11]-nitromethane and 2′-[C-11]-2,2′-dinitrophenylethene (**11**) by $TiCl_3$ reduction.[33,34] Wittig-type reagents offer a range of chemistry by which [C-11]-labelled alkenes, for example, may be produced.[35]

Labelled *diazomethane*, prepared from [C-14]-methyl iodide, has been used as a methylating agent, as in the synthesis of [21-C-14]-fusarin-C (**12**).[36,37] The Gabriel synthesis of [C-14]-methylamine, its subsequent reaction with tosyl chloride, and *N*-nitrosation of the resulting amide



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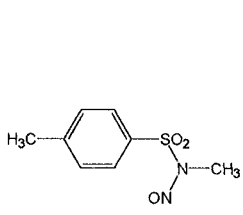

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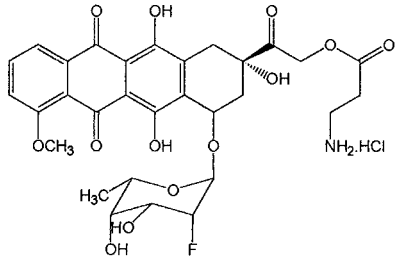

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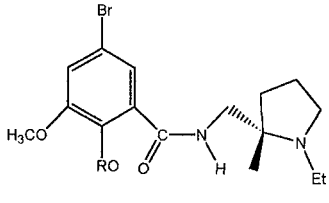
gives *N*-([C-14]-methyl)-*N*-nitroso-*p*-toluene-sulfonamide (**13**). The Arndt–Eistert reaction was successfully applied to form the diazo-ketone ($R \cdot CO \cdot {}^{14}CHN_2$) which gave esters with alcohols, or the bromomethyl ketone with HBr. Such a sequence was used in a synthesis of labelled DA-125 (14-*O*-(*β*-alanyl-*N*-HCl)-7-*O*-(2′,6′-dideoxy-2′-fluoro-*α*-L-talopyranosyladriamycinone; **14**).[38] The wider use of diazomethane, labelled with the more stable isotopes, should be encouraged. Interestingly, **13** labelled at the 4-methyl position (**13a**) has been reported; the isotopic label was incorporated through a Suzuki reaction between [C-14]-methyl borinate and 4-iodobenzenesulphonic acid.[37]

Iodomethane is usually the most rapidly reacting methyl halide in the S_N2 processes which characterize *N*-, *O*-, and *S*-methylation. For example, [C-11]-methyl iodide alkylates –OH groups when used in the presence of NaOH in DMSO at 80° for 3 min, and [C-11]-FLB 457 (**15b**; $R = {}^{11}CH_3$) is obtained from FLB 604 (**15a**; R = H) by *O*-methylation in 25–35% radio-chemical yield and 1300 Ci mmol^{-1} specific activity in



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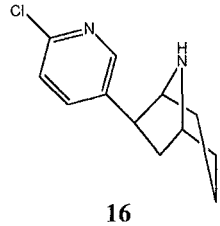

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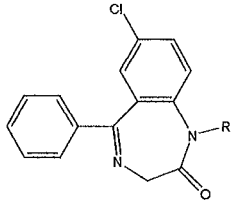
30 min synthesis time.[39,40] Radio-chemical yields in such alkylations are often poor when alkoxide and not phenoxide ion is the effective nucleophile. Again, the attack by [C-11]-methyl iodide upon homo-epibatidine (**16**) proceeds in 5–10% radio-chemical yield.[41] In some cases, the pre-formation of an isolated anionic reagent improves the radio-chemical yield. In the preparation of *N*-([C-11]-methyl)-diazepam (**17b**; $R = {}^{11}CH_3$), pre-formation[42] of the sodium salt of desmethyldiazepam (**17a**; R = H) and isolation of its complex with benzo-15-crown-5 avoided the side reactions, such as the formation of



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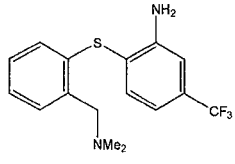

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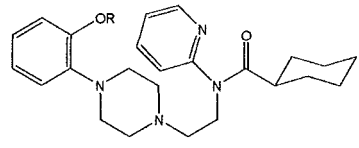

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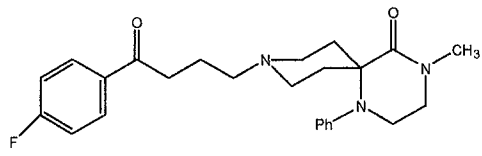
[C-11]-methanol, associated with the earlier use[43] of 10 M NaOH in acetone with mixtures of the desmethyl compound and [C-11]-methyl iodide. In contrast, *O*-methylation ([C-11]-methyl iodide) using tetra-butylammonium hydroxide in DMF has been reported to occur in 85% radio-chemical yield.[44] Similarly, [C-11]-methylation ([C-11]-CH_3I – DMF) of the *nor*-compounds gave labelled *N*,*N*-dimethyl-2-(2-amino-4-trifluoromethylphenylthio)benzylamine (**18**) and its monomethyl analogue,[45] and *N*-{2-[4-(2-hydroxyphenyl)-1-piperazinyl]-ethyl}-*N*-(2-pyridinyl)cyclohexanecarboxamide (**19**, R = H) under similar conditions gave the [C-11]-labelled 2-methoxy-derivative (WAY-100635, **19**, $R = CH_3$).[46]

Methyl triflate (methyl trifluoromethylsulphonate, $CF_3 \cdot SO_2 \cdot O \cdot CH_3$*)* has been introduced as an even more fast methylating agent.[10,11,18,19,47,48] As mentioned earlier, radiolabelled methyl triflate is generally obtained by the reaction of methyl halide with silver triflate; for example, a gas stream containing [C-11]-methyl iodide impinges upon silver triflate absorbed upon graphite at loadings as high as 50% at 170–200°. Methyl triflate so obtained (750 mCi; 960 mCi EOB from 1.20 Ci of carbon dioxide at EOB; 80% yield after decay correction) was allowed to react with a desmethyl compound to give the [C-11]-methyl analogue very quickly.[49] The methylating agent which is present in the condensed reaction product shows both a higher reactivity and a more selective attack upon *N*-, *S*- and *O*-based nucleophiles.[6]



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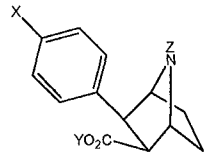

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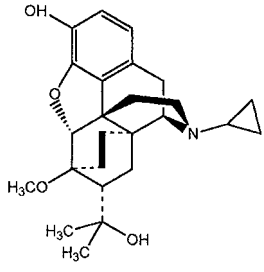
Halldin and his colleagues[50–57] reported the preparation of [C-11]-NMSP (**20**),[4] [C-11]-flumazenil (**7**)[50] and [C-11]-methionine (**5**)[50] in 50–75% radio-chemical yield, and of [C-11]-β-CIT (**21a**, X = I; Y = Z = H),[51] where either *O*- or *N*-methylation may be achieved,[52] L-[C-11]-deprenyl (**22**),[51] [C-11]-*m*-hydroxyephedrine (MHED),[51] [C-11]-SCH-39166, [C-11]-NNC-112,[53] and [C-11]-β-CFT-FP (**21b**, X = F; Z = F · CH_2 · CH_2–).[54] They found[50] that methyl triflate required smaller excesses of reactant, shorter reaction times, and lower reaction temperatures than did methyl iodide.



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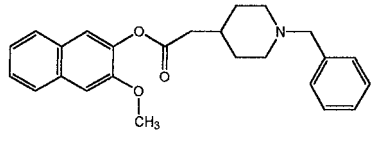
It was also compatible with low concentrations of aqueous sodium hydroxide, which reduced the extent of formation of D-methionine in the methylation of L-homocysteine thiolactone. Dimethylformamide was used as a solvent in the KOH-mediated [C-11]-methylation of 3-



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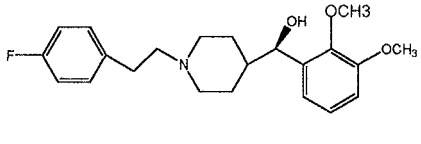

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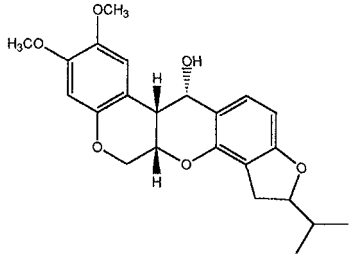
hydroxynaphth-2-yl(1-benzylpiperidin)-4-yl acetate by methyl triflate in a synthesis of [C-11]-SB-235753 (**23**; 1000 + 300 Ci mmol^{-1}), though the radio-chemical yield (10%) suggests some side reactions.[58]

Methylation of phenols, as in the syntheses of [C-11]-FLB 457 ((*O*-methyl-[C-11])-(*S*)-5-bromo-*N*-((1-ethyl-2-pyrrolidinyl)methyl)-2,3-dimethoxybenzene, **15b**), [C-11]-MDL 100907 ((3-*O*-methyl-[C-11]-(*R*)-(+)-4-(1-hydroxy-1-(2,3-dimethoxyphenyl)-methyl)-*N*-2-(4-fluorophenyl)-ethyl)-piperidine, **24**),[55,59] and (2-[C-11]-methoxy)-6′,7′-dihydroroten-12α-ol (**25**),[60] and the formation of labelled methyl esters such as [C-11]-β-CIT-FE (2β-carbomethoxy-*N*-(2-fluoroethyl)-3β-(4-iodophenyl)tropane (X = I, Y = CH_3, Z = F · CH_2 · CH_2–; **21c**), proceed more quickly and in better radio-chemical yield than with methyl iodide.[56]



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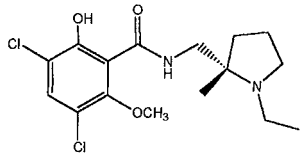

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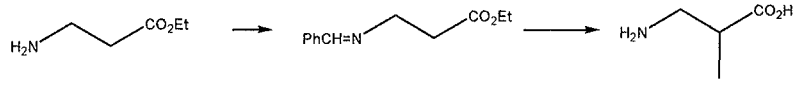
However, the exchange between methyl iodide and silver triflate does not always seem to be complete, as the reported conversion yields imply. Recently, in an automated synthesis of [C-11]-raclopride (**26**, 1500–2000 Ci mmol^{-1}; 65–75% radio-chemical yield; 35 min after EOB),[57] methylation by [C-11]-methyl triflate generated in this way was found to be accelerated by the presence of silver acetate. This may be most readily explained by suggesting that both methyl iodide and methyl triflate were present in the alkylating reagent, and that the silver salt then assisted the heterolysis of the C–I bond in the former reagent. [C-11]-methyl acetate was formed when silver acetate, but not silver triflate, was present. This supports this suggestion, though the radio-chemical yield of the methylated drug in the presence of silver triflate was not appreciably increased, and methyl acetate might have arisen from the reaction between silver acetate and methyl triflate. Presumably, the same behaviour is to be expected of methyl triflate formed from bromomethane, reported to be achieved in 80–90% yield.[18]

The next sections deal with the isotopic methylation of some of the more common carbon-, oxygen-, nitrogen-, and sulphur-based nucleophiles.

C-[C-11]-methylation. The relatively short half-life of carbon-11 discourages syntheses which rely upon carbon-based nucleophiles.

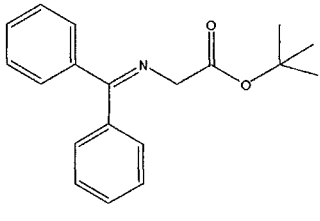
Other functional groups usually need protection in such processes, and this introduces two extra steps (protection and deprotection) during which the specific activity of the labelled substance may fall considerably. An example, both of the difficulties which such synthetic sequences suffer and of the possible successes, is found in the synthesis of [C-11]-2-aminoisobutyric acid (**29**).



27 **28** **29**

Ethyl 2-aminopropionate (**27**) was converted into the benzaldimine derivative (**28**, 87%). Deprotonation by LDA in THF at −78°, followed by MeI, provided the α-methyl derivative. Acid hydrolysis deprotected the amino function; base hydrolysis of the ester gave the free aminoacid. The total yield of the sequence, using unlabelled reagents, was 37%. When [C-11]-methyl iodide was used, the decay-corrected radiochemical yield was 20–60% of material with an average specific activity of 450 Ci mmol^{-1}. The enantiomers could be cleanly separated on a chiral column cooled by ice-water, eluting with aq. $HClO_4$ (pH, 1.05), when the (*S*)-isomer was obtained after 17.4 min and the (*R*)-isomer after 20.0 min.[61]

The Schiff's base from glycine and (*S*)-2-*N*-(*N*′-benzylprolyl)aminobenzophenone forms a nickel complex which may be [C-11]-methylated at room temperature in the presence of base. The product, in which the (*S*,*S*)-diastereomer predominates over the (*S*,*R*)-form, may be rapidly hydrolysed to give mixtures of [3-C-11]-D- and -L-alanine in which L-alanine is the major component. By hydrolysing with KOtBu, [3-C-11]-L-alanine may be obtained quickly (1 min) in 99% e.e.[62] In a similar process, [C-11]-methyl iodide alkylates *N*-(diphenylmethylene)glycine *t*-butyl ester (**30**) to provide [C-11]-DL-alanine.[24]



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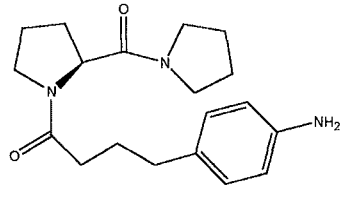

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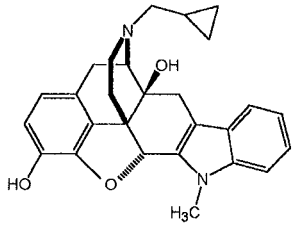
N-[C-11]-methylation[63,64]. 2-Dimethylaminoethanol behaves as both nucleophile and reaction solvent in the preparation of [C-11]-choline from the reaction with [C-11]-methyl iodide.[12,27,65] *N*-[C-11-methyl]-isovaleroyl-L-carnitine is obtained using [C-11]-iodomethane; [H-3(3)]-iodomethane gives the analogous isotopomer.[66] The [C-11]-methylation of three drugs is also reported.[67]

N-{*N*-[4-(4-Aminophenyl)butyryl]-L-prolyl}pyrrolidine (**31**, SUAM-1221) with CH_3I provides a mixture of the mono- and di-methylamino derivatives which may be separated by column chromatography. [C-11]-Iodomethane leads to the 4-([C-11]-methylamino)phenyl derivative in 18–30% yield, at an activity of 1700 Ci mmol^{-1}, during a 40-min synthesis.[68]

In the synthesis of *N*1′-(([C-11]-methyl)-naltrindole (**32**, MeNTI) the phenolic function was protected by benzylation (71% yield) before the indole nitrogen atom was [C-11]-methylated ([C-11]-CH_3I, $Bu_4N^+OH^-$, aq. DMF, 80°C). Hydrogenolysis (10% Pd/C, H_2) then cleaved the benzyl group in a total time of 24 min from EOB. The radio-chemical yield from iodomethane was 6%, and the specific activity of the product was 2050 Ci mmol^{-1}.[69]

2*β*-Carbomethoxy-3*β*-(4-fluorophenyl)-*N*-([C-11]-methyl)-tropane (**21d**; X = F, Y = CH_3, Z = CH_3) is reported to be formed by methylation ([C-11]-CH_3I – DMF) of the nor-precursor, derivatization with a long-chain acyl halide, and purification by HPLC. This process gave material of high specific activity (3065 Ci mmol^{-1}) in 21 min.[70]



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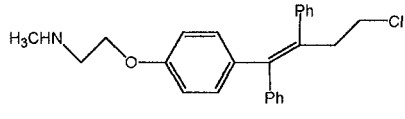

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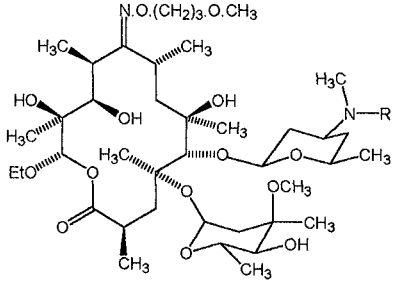
N-([C-11]-methyltoremifene (**33**, *N*-([C-11]-methyl)-(*Z*)-2-(4-(4-chloro-1,2-diphenyl-1-butenyl)-phenoxy)-*N*-methylethylamine) was obtained in 55–65% radio-chemical yield by alkylation of the desmethyl precursor with [C-11]-methyl iodide.[71] *N*-([C-11]-methyl)-roxithromycine (**34**) was similarly obtained in good yield (40–45%) and high specific activity (500–550 Ci mmol^{-1}) from the normethyl analogue,[72] as was (*S*)-3-([C-11]-methyl)-5-[1-methyl-2-pyrrolidinyl]isoxazole (**35**, ABT-418), *N*-([C-11]-

methyl)-1,2,3,4,5,6-hexahydro-1,5-methano-8H-pyrido-[1,2-a][1,5]-diazocin-8-one) and (+)-(*E*)-(1*R*,2*R*,3*S*)-3-(3,4-dichloro-phenyl)-8-([C-11]-methyl)-8-azabicyclo-[3.2.1]octane-2-*O*-methyl aldoxime (**37**, NS 2214 or BMS 204756; 24–30%; specific activity > 1400 Ci mmol^{-1}, 30 min after EOB).[74]



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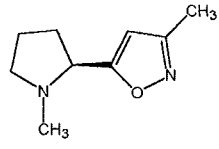

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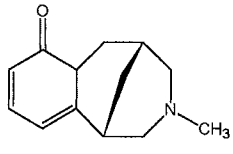

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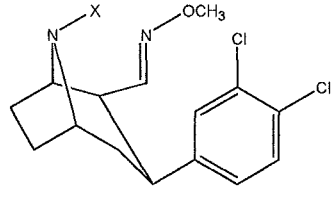

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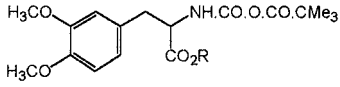
[C-11]-MK912 was obtained from the desmethyl analogue (L-668,929 through [C-11]-methyl iodide in the presence of tributyl phosphate. The labelled drug was obtained in 18% yield and 97% radio-chemical purity 45 min after EOB in specific activities of 830–930 Ci mmol^{-1}.[75]

N-methylation of the methyl or ethyl esters of *N*-tert-butyloxycarbonyl-L-[*β*-(3,4-dimethoxyphenyl)]-alaninate (**38**) with [C-11]-iodomethane (NaH in THF; Kryptofix) followed by deprotection with HI gave *N*-([C-11]methyl)-L-DOPA in a specific activity of 972 Ci mmol^{-1} and an overall reaction time of 45 min (ethyl ester).[76] The corresponding *N*-methylation with [C-11]-iodomethane of *N*-nor-methyldoxepin gave *N*-[C-13]doxepin (**39**, 3-dibenz[b,e]oxepin-11(6H)-ylidene-*N*,*N*-dimethylpropanamine). The process took 20 min, giving material of average activity 1630 Ci mmol^{-1} (EOS).[‡77] Again, 1-(2-bromo-4,5-dimethoxybenzyl)-7-hydroxy-6-methoxy-2-([C-11]-methyl)-1,2,3,4-tetrahydroisoquinoline ([C-11]-A-69024, **40**) is achieved by the reaction of

[‡] End of synthesis, usually beginning at the end of bombardment of the target.



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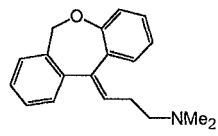

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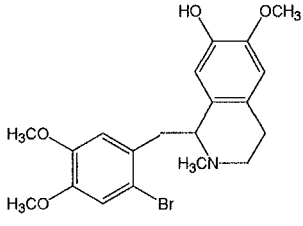
N-desmethyl A-69024 with [C-11]-methyl iodide in DMF.[78] The 20-min synthesis provided material whose specific activity was 1950 Ci mmol^{-1}. The synthesis of *N*-([C-11]-methyl)-*N*-(*trans*-2-pyrrolidinylcyclohexyl)-3,4-dichlorophenylacetamide (U-50488H, **41**) was achieved by a two-step or a single-step methylation using [C-11]-iodomethane. The single-step process, although quicker (average time, 22 min), gave material of lower specific activity (1830 Ci mmol^{-1} EOS) than did the two-step process (2140 Ci mmol^{-1} EOS; 27 min).[79]



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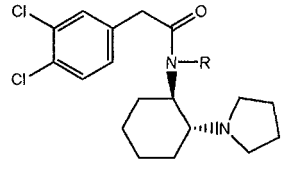

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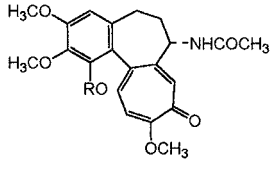
(−)-Desmethylcolchicine, methylated with [C-11]- or [C-13]-labelled methyl iodide, gave (−)-10-[C-11 or C-13]-colchicine (**42**) and



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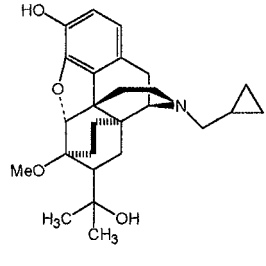

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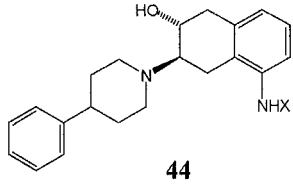

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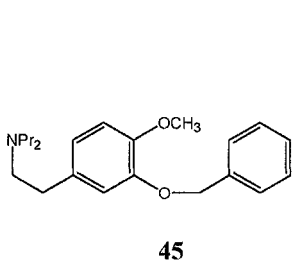
(−)-9-[C-11 or C-13]-isocolchicine. Either process took 60 min, giving products with specific activities of 240 Ci mmol^{-1}.[80] Likewise, [C-11]-diprenorphine (**43**),[81] [C-11]-NNC 22-0215[82] and [C-11]-Ro5-4864[83] were labelled using [C-11]-iodomethane.

([C-11]-methylamino)benzovesamicol (**44**, MABV) is obtained by activating the aniline nitrogen atom towards [C-11]-methyl iodide in basic conditions through *t*-butyloxycarboxylation. Brief acid treatment removes the Boc group giving yields of 30–70% based upon [C-11]-carbon dioxide, with a specific activity of 500–1500 Ci mmol^{-1} and a synthesis time of 45 min EOB.[84]

The [C-11]-labelling of NE-100 (*N*,*N*-dipropyl-2-[4-methoxy-3-(2-phenyl-ethoxy)phenyl)]ethylamine, **45** has been achieved both by *N*-alkylation of the despropyl precursor with [2-C-11]-isopropyl iodide and by *O*-[C-11]-methylation (iodomethane) of the 4-hydroxyphenyl analogue.[85] Similarly, [C-11]-methylation of the desmethyl precursor lead to 3-(*R*)-(+)-*N*-(2,3-dihydro-1-([C-11]-methyl)-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-*N*′-(3-methylphenyl)urea ([C-11]-L-365,260, **46**), and [C-11]-L-365,346, its (*S*)-enantiomer, which were separated by HPLC.[86] 2,5-Dimethyl-3-(4-fluorophenyl)-1-([1-C-11]-methyl-4-piperidinyl)-1*H*-indole ([C-11]-Lu29-024, **47**) was made from the precursor



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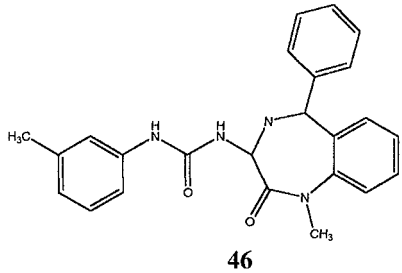

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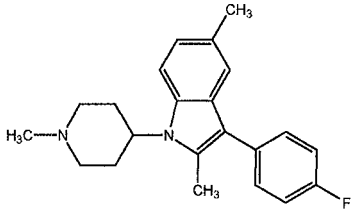

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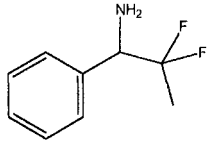

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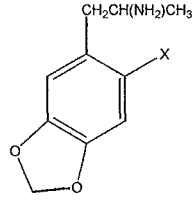

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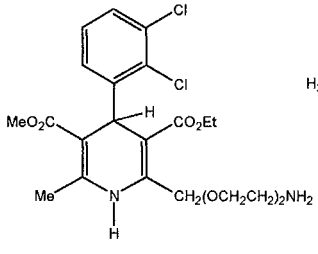
and [C-11]-methyl iodide in specific activities of 300–400 Ci mmol^{-1} and in 35–50% radio-chemical yield after 45–50 min.[87] Both (*R*)- and (*S*)-$\beta\beta$-difluoromethamphetamine (**48**) may be [C-11]-methylated using the

iodide. Corrected radio-chemical yields over 35 min are 15–16% of material with specific activites of 1300–4000 Ci mmol^{-1}.[88] (*N*-[C-11]-methyl)-3,4-methylenedioxyamphetamine ([C-11]-Ecstasy, **49a**, X = H) and 2-methyl-(*N*-[C-11]-methyl)-4,5-methylenedioxyamphetamine (**49b**, X = CH_3) have analogously been prepared from [C-11]-methyl iodide over 10 min in a 60% radio-chemical yield.[89]

3-Ethyl-5-methyl-2-[2-aminoethoxy)ethoxymethyl]-4-(2,3-dichlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (**50**) may be labelled by [C-11]-methyl iodide to give [C-11]-S11568.[90] While most such *N*-methylations use typical S_N2 reaction conditions (ionising solvents; 25–50°), the synthesis of *N*-[C-11]-methylated halogeno-analogues of *N*-methylepibatidine, (±)-*exo*-*N*-methyl-2-(2-X-5-pyridyl)-7-azabicyclo[2.2.1]heptanes (**51**, X = F, Cl, Br), involved high temperature/high pressure techniques.[91] In contrast, *N*-[C-11]-methyl-3β-(4′-chlorophenyl)-2β-(3′-phenylisoxazol-5′-yl)tropane (**52**) is obtained at high specific activity (2000–2700 Ci mmol^{-1} at EOS after 60 min) by [C-11]-methylation of the desmethyl precursor.[17]



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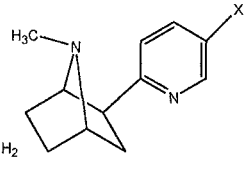

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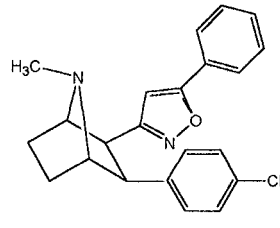

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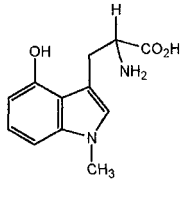
[C-11]-Psilocin (900–2300 Ci mmol^{-1} at EOS, 45 min after EOB) is obtained by the [C-11]-methyl iodide alkylation of 4-hydroxy-*N*-methyltryptamine (**53**).[92]

O-*[C-11]-methylation*. Analogues of WAY 100635, such as *N*-[(2-(4-(2-([C-11]-methoxy)phenyl))-1-piperazinylethyl] [*N*-(2′-pyridinyl)] bicyclo-[2.2.2]-octanecarboxamide (**54**),[93] and the *trans*- and *cis* isomers of



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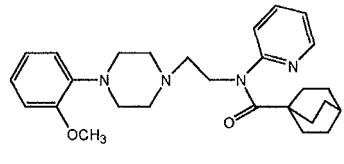

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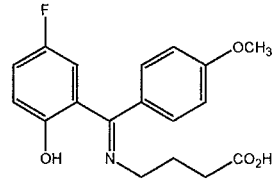
N-[2-[4-(2-([C-11]-methoxy)phenyl)-1-piperazinylethyl] [*N*-(2-pyridinyl)] cyclohexanecarboxamide (**19**), were obtained by *O*-alkylation of the hydroxy-compounds. Although the specific activities are high, the yields are poor.[94]

5-Fluoro-2,4′-dihydroxybenzophenone, obtained by demethylation of the 4′-methoxy analogue (BBr_3), could be selectively and specifically methylated ([C-11]-methyl iodide/alkali; 27% radio-chemical yield) at the 4′-hydroxyl function. Condensation of this 5-fluoro-2-hydroxy-4′-([C-11]-methoxy)benzophenone with GABA gave 4-({4-([C-11]-methoxy)phenyl}-{5-fluoro-2-hydroxyphenyl}methylene-amino)butyric acid (**55**; 20 mCi; 100 Ci mmol^{-1}; 45 min from EOB).[95] *O*-Methylation of the *N*-protected *dl-threo*-ritalinic acid by [C-11]-methyl iodide and deprotection gives labelled methylphenidate (methyl 2-phenyl-2-(2-piperidyl)acetate, Ritalin, **56**).[96] Similarly, the individual [C-11]-labelled enantiomers may be obtained from *d* or *l-threo*-ritalinic acid, in about 40% radio-chemical yield with a specific activity of 1500 Ci mmol^{-1} and a total reaction time after bombardment of 40 min. [C-11]-4-Carbomethoxyfentanyl (methyl *N*-(2-phenylethyl)-4-[*N*-(1-oxopropyl)-*N*-phenylamino]-4-piperidinecarboxylate, **57**[97] could be similarly obtained,[59]



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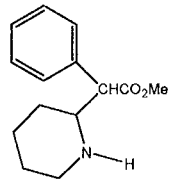

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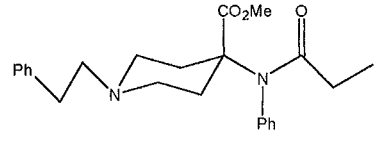

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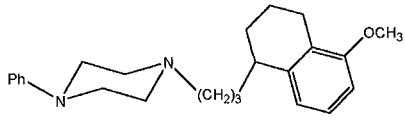

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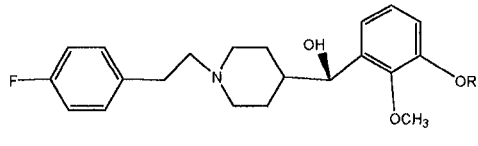

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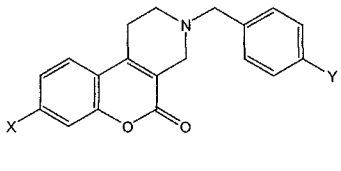
while (*R*)-(*O*-[C-11]-methyl)metomidate and (*R*)-(*O*-[1-C-11]-ethyl)etomidate arise from alkylation of the tetrabutylammonium salt of the carboxylic acid using the appropriate alkyl iodide.[98] Racemic PNU-157760 (1-[3-(5-[C-11]-methoxy)-1,2,3,4-tetrahydro-1-naphthalenyl]propyl-4-phenylpiperazine, **58**) with specific activity of 1500–3500 Ci mmol^{-1} is obtained from the inactive material by demethylation (BBr_3) and treating with [C-11]-methyl iodide.[99] [C-11]-methylation by

iodomethane has also been reported in the synthesis of *R*-(3-{4-[*N*-(2-(4′-fluorophenyl)ethyl)]-piperidinyl](hydroxymethyl)})-(1-[C-11]-methoxy)-1,2-dimethoxybenzene (**59**, $R = CH_3$),[100] and of 3-(4-chlorobenzyl)-8-([C-11]-methoxy)-1,2,3,4-tetrahydrochromeno-[3,4-c]pyridin-5-one (**60**, R = Cl) and its 3-(4-trifluoro-methylphenyl) analogue (**60**, $R = CF_3$).

([C-11]-methoxy)-PD153035 (**61b**) was obtained in 45% radiochemical yield from [C-11]-methyl iodide and *O*-desmethyl-PD153035 (**61a**) in DMF.[101] More recently, 1-benzyl-4-[((6-[C-11]-methoxy)-5,6-dimethoxy-1-oxoindan-2-yl)methyl]piperidine (Donepezil, **62**)[102] and



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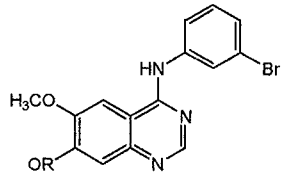

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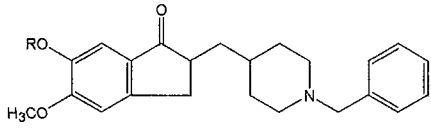

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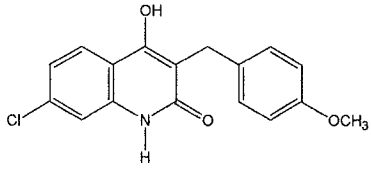
3-([C-11]-methyl)-(3-methoxynaphthalen)-2-yl-(1-benzyl-piperidin)-4-yl acetate (**23**)[58] have been similarly prepared. Remarkably good yields are reported from the use of NaH in DMF as the deprotonating agent. 7-Chloro-4-hydroxy-3-[3-(4-[C-11]-methoxy)benzyl)-phenyl-2(1*H*)-quinolone ([C-11]-L-703,717, **63**) was obtained in 87% chemical yield (99% radio-chemical purity), 25 min after EOB and with a specific activity of 1270–1430 Ci mmol^{-1} after treatment with [C-11]-methyl iodide at 30° over 5 min.[103]



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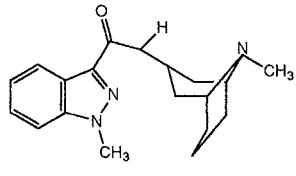

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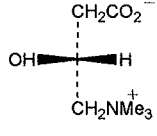
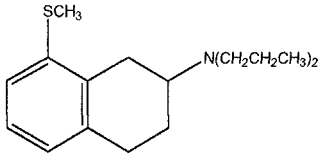


65

The synthesis of labelled 2β-carbomethoxy-3β-(4-methylphenyl)tropane (**21**; X = Y = Z = CH_3) and its 4-chlorophenyl (**21**, X = Cl; Y = Z = CH_3) analogue by *O*-alkylation ([C-11]-iodo-methane) of the carboxylic acid gave material of high specific activities (800–3000 Ci mmol^{-1}) and was superior to processes based upon *N*-methylation.[104] Earlier similar work reported the labelling of the 3-(4-iodophenyl) analogue with [C-11] and [H-3].[105] [C-11]-granisetron (**64**; 250 Ci mmol^{-1}; 96% chemical purity; 98% radio-chemical purity) also may be prepared from the desmethyl precursor using [C-11]-CH_3I in a total reaction time of 40 min.[106]

Methylation ([C-11]-CH_3I) of the desmethyl analogue gave [C-11]-(*R*)-carnitine (**65**).[107]



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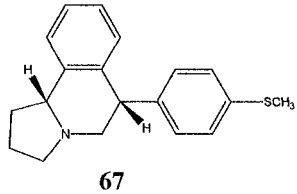
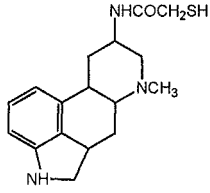


67

S-[C-11]-methylation. [C-11]-LY274601 (**66**, (*R*)-(+)-8-thiomethoxy-2-(di-*N*-propylamino)tetralin) was made by alkylation of the 8-thiol in DMF with [C-11]-iodomethane at 40°C, having unmasked the –SH function by hydrolysis of the butyrate thioester. The average radio-chemical yield in the 30-min process was 36 ± 10% The specific activity of the product was 630 ± 80 Ci mmol^{-1}; reaction with [H-3(3)]-iodomethane similarly gave the tritiated analogue.[108]

trans-1,2,3,5,6,10b-Hexahydro-6-[4-([C-11]methylthio)phenyl]-pyrrolo-[2,1-a]-isoquinoline (McN-5652-Z, **67**) was obtained from the normethyl precursor with an average specific activity of 4250 Ci mmol^{-1} and a radio-chemical yield of 12%, using [C-11]-iodomethane in DMF at 30–35°C. The process took an average of 16 min and was also successfully applied to prepare the *cis*-isomer, [C-11]-McN-5655-Z.[109] A stereoconservative route to the precursors of [C-11](+)-McN-5652 and [C-11](−)-McN-5652 ([C-11] McN-5652-X and [C-11]-McN-5652-W, alternatively) relies upon the transformations of the *trans*-4-bromophenyl analogues of (+)- or (−)-McN-5652 firstly to the tri(isopropyl)silyl thioethers (R_3Si-S-R′) and thence, by deprotection and acylation in a one-pot sequence, to benzoyl thioesters. The tartrate salts of these esters then gave arylsulphide systems whose rapid *S*-methylation was

accomplished by [C-11]-methyl iodide. The desired enantiomers were obtained with specific activities of 4000 Ci mmol^{-1} and in yields of *ca* 120 mCi.[110] The sodium salt of *N*-(mercaptoacetyl)-8α-amino-6-methylergoline (**68**) gave the expected ([C-11]-methylmercapto)acetyl derivative with [C-11]-methyl iodide.[111]



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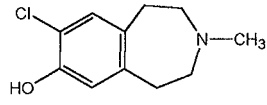


69

A high efficiency preparation of (*S*)-([C-11]-methyl)-L-methionine (**5**) has been recently reported; methylation on C18 Sep-Pak is an essential feature,[112] as in the synthesis of [C-11]-WAY 100635 (**19**, R = CH_3).[42] Another such system, reported to make [C-11]-iodomethane in 10.5 min, prepares ([C-11]-methyl)-L-methionine (**5**) in yields of 25% (decay-corrected) and over 30–35 min in total.[113]

[C-13]- and [C-14]-methylation

In a reversal of the methods used to prepare [C-11]-iodomethane, [C-14]-methane may be obtained from [C-14]-iodomethane by $NaBH_4$ reduction.[114]

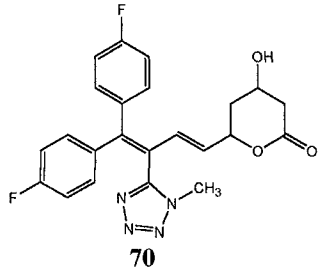
N-methylation. *N*-methylamines are also available from isotopically labelled methyl iodide through a quaternization/dequaternization process which need not involve isotopic dilution of the label, but which, because it relies upon the thermodynamics of the system and not its kinetics, may not be suitable for incorporating radiolabels such as carbon-11.[115]

The methylation of xanthine with [C-13]-methyl iodide provided 3- and 7-methylxanthines, and 1,3- , 1,7- and 3,7-dimethylxanthines (theophylline, paraxanthine, and theobromine, respectively), with labelled carbon in each methyl group.[116] (+)-8-Chloro-5-(2,3-dihydrobenzofuran-7-yl)-7-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (NNC 756, **69**) was obtained in 11% radio-chemical yield from [C-14]-methyl iodide. The specific radioactivity was 24 mCi mmol^{-1}.[117] In a patent, an *N*-Boc derivative of a piperidine system was deprotected

(CF_3CO_2H–CH_2Cl_2, 16 h, r.t.) to allow *N*-methylation by [C-14]-methyl iodide.[118]

Lyophilized protein may be methylated by [C-14]-methyl iodide either in vacuo or using dispersions in octane. Three general types of reaction were identified: quaternization of $-NMe_2$ functions, the formation of *N*,*N*′-dimethylimidazolinium cations, and the methylation of phenolic functions. The advantages of these conditions include the isolation of water-soluble and water-labile materials as solid derivatives, so minimizing hydrolytic breakdown of the proteins.[119]

trans-6-[4,4-*bis*(4-Fluorophenyl)-3-(1-methyl-1H-tetrazol-5-yl)]-1*E*,3-[2-C-14]-butadienyl-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (BMY-22089, **70**) is obtained by the reaction of [C-14]-methyl iodide with 1,5-dimethyltetrazole. The product, with 4,4′-difluorobenzophenone, gave a tertiary alcohol which, after dehydration, bromination, and conversion to the phosphonate ($(MeO)_3P$) forms a carbanion. This couples with *t*-butyl *cis*-2,2-dimethyl-6-formyl-1,3-dioxan-4-acetate (**71**) to give the required lactone after hydrolysis steps and then dehydration of the dihydroxyacid with dicyclohexylcarbodiimide.[120] The overall yield is 20%.



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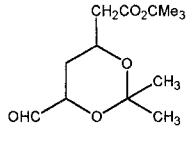

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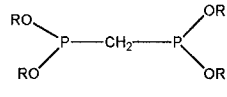


72

Under photolysis, methylcobalamin gives formaldehyde. Using [C-13]-methyl iodide to alkylate vitamin B_{12} showed the source of this aldehyde to be the methyl group.[121]

Both [N-15] and [C-13] have been incorporated into *N*-[*N*-(diphenylmethylene)glycinyl]camphorsultam using [N-15]-ammonium chloride, potassium [C-13]-carbonate, [C-13]-methylamine, or labelled glycine as sources of the isotope. Alkylation by appropriate electrophiles gave a range of labelled aminoacids.[122]

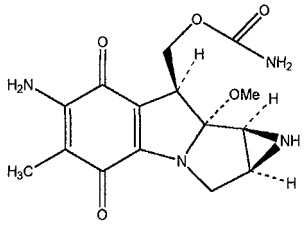
O-methylation. Tetra*kis*(1-methylethyl)methylene-*bis*-phosphonate was obtained by the Michaelis–Arbuzov reaction of [C-13]-methyl iodide

with *tris*(1-methylethyl)-phosphonate, followed by reaction with *bis*(1-methylethyl)chlorophosphonate. Tetra*kis*(1-methylethyl)([C-14]-methylene)*bis*phosphonate (**72**; $R = (CH_3)_2CH–$) was obtained from [C-14]-dibromomethane by the Michaelis–Arbuzov reaction with an excess of *tris*(1-methylethyl)phosphite. Labelled clodronate (disodium (dichloromethylene)*bis*phosphonate) was made by chlorination with NaOCl, hydrolysis of the ester functionality with HCl, and neutralization (NaOH). The [C-13]-enriched material was obtained in 71% overall yield, 99.8% chemical purity and 99.5% isotopic purity; the [C-14]-labelled product was obtained in 9.8% radio-chemical yield.[123]

[C-14]-methyl iodide provides 3-([C-14]-methyl)anisole, 3-([C-14]-methyl)-phenol, 3-([C-14]-methyl)-Metacresol Purple and [C-14]-Bromocresol Green. The specific activity of the Bromocresol Green is 112 mCi mmol^{-1}, and the radio-chemical yield from iodomethane is 5.3%.[124]

Mitomycin C (**73**) may be labelled[125] with carbon or hydrogen isotopes at the methyl group attached to C_6 by demethylation followed by alkylation of 6-desmethyl-7,7-(ethylenedioxy)-6-(phenylselenyl)mitosane using [C-14]- or [H-3(3)]-methyl iodide. The phenylselenyl substituent is removed and the product is treated with ammonia to give the desired [C-14]-labelled material with activities of 50 mCi mmol^{-1}. The corresponding tritium-labelled material is obtained at higher specific activities of 78.4 Ci mmol^{-1}.

The similar synthesis of (3-[C-14]-methoxy)-sinapic acid[126] at 54 mCi mmol^{-1} was achieved by the appropriate methylation of methyl 3-(4-benzyloxy-3-hydroxy-5-methoxyphenyl)-2-propenoate (**74**). Cleavage of the benzyloxy function and hydrolysis of the ester were achieved quantitatively.



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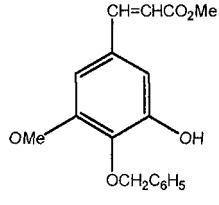
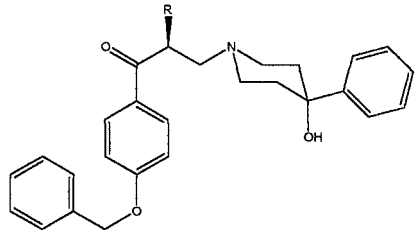


74

S-methylation. A synthesis of [C-13(2)]-DMSO, starting from commercially available [C-13]-methyl iodide, proceeds in 57% yield and gives

material of high chemical (>99%) and high isotopic purity (98% C-13(2), 2% C-13(1)).[126] The synthesis of labelled 2-chloroethyl methyl sulphide by reaction between [C-13]-methyl iodide and 2-chlorothioethanol was complicated by concomitant reaction with iodide ion, the inorganic product of the desired alkylation. This was resolved by a two-step process in which the methylation of mercaptoethanol ($HS \cdot CH_2 \cdot CH_2OH$) was followed by reaction with thionyl chloride.[128]

C-methylation and other alkylations. Landvatter[129] has investigated the use of SmI_2 as an alternative to magnesium in the alkylation of aldehydes and ketones by [C-14]-methyl iodide. THF containing a small amount of HMPA gave 75–90% yields of alcohols arising from reductive methylation of aldehydes and ketones, but rather poorer results with aromatic aldehydes. Although somewhat more selective, and more liable to give pinacolic products, samarium(II) iodide has some clear advantages and deserves to be applied to further radio-chemical syntheses. Methylation of 1-(4-benzyloxy)phenyl-2-(4-hydroxy-4-phenylpiperidin-1-y1)-ethan-1-one (**75**, R = H) by [C-14]-iodomethane has also been used to introduce the radiolabel, giving 1-(4-benzyloxyphenyl)-2-(4-hydroxy-4-phenylpiperidin-1-y1)-[3-C-14(1)]-propanone (**75**, $R = {}^{14}CH_3$).[130]



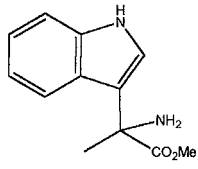
75

Alkylation is similarly achieved using ethyl [1,2-C-13(2)]-bromoacetate with DIBAL (diisobutylaluminium hydride) in dichloromethane, followed by reaction with triphenylphosphine, and then triethylamine, which provides [1,2-C-13(2)]-formyl-methylenetriphenylphosphorane. Wittig reactions, firstly with methyl (5*S*,6*R*)-epoxy-6-formylhexanoate and then with Z-3-nonen-1-triphenylphosphorane yields the methyl ester of [8,9,10,11-C-13(4)]-LTA4, which is readily converted into [8,9,10,11-C-13(4)]-LTC4.[131]

Derivatives of perillic acid (4-isopropenylcyclohexene-1-carboxylic acid) may be obtained from commercially available (4*S*)-(−)-perillaldehyde.

Protection of the aldehyde function (ethylene glycol) and oxidation ($NaIO_4$–OsO_4) gives an acetyl function in place of the isopropenyl group at C-4. The Wittig reaction with triphenylphosphine and either [H-2(3)]-methyl iodide or [C-13; H-2(3)]-methyl iodide then provides a protected equivalent of perillaldehyde in which the $=CH_2$ function of the isopropenyl group has two deuterium substituents and either [C-12] or [C-13].[132] After deprotection, the resulting aldehyde function may be reduced by deuteriated LAH to incorporate further deuterium into the resulting alcohol.

α-([C-11]-methyl)-tryptophan (**76**) and its methyl ester were obtained from α-deprotonation of tryptophan methyl ester benzaldimine (**77**) by LDA, and alkylation with n.c.a. [C-11]-methyl iodide (5 min; 27–30°C, 60–80% incorporation). Although radiochemically pure, the α-([C-11]-methyl)tryptophan was racemic.[133]



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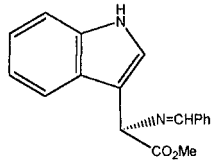

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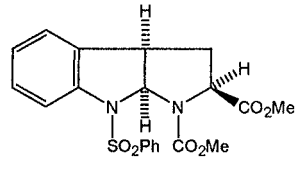


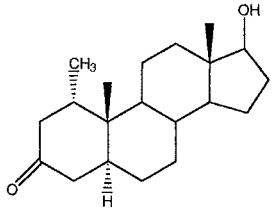
78

LDA deprotonates dimethyl (2*S*,3a*R*,8a*S*)-(+)-8-(phenylsulfonyl)-hexahydropyrrolo-[2,3-b]indole-1,2-dicarboxylate (**78**); the resulting anion may be methylated using either [C-14]- or [H-3(3)]-iodomethane to yield, after hydrolysis, the correspondingly labelled α-methyl-L-tryptophan.[134] [Vinyl-C-14]-chlorfenvinphos was prepared by the reaction of 2,4-dichlorobenzoyl chloride and [C-14]-iodomethane (28% radio-chemical yield). Side-chain chlorination of the resulting [2′-C-14(1)]-2,4-dichloro-acetophenone and then reaction with triethyl phosphite gave a mixture of *E*- and *Z*-isomers (4 : 96) of >99% purity and a reported specific activity of 20 mCi/mmol.[135]

[C-13]-methylated thymidine may be obtained by the alkylation of *t*-butyldimethyl-silyl-protected 2′-deoxyuridine.[136]

Lithium(2-thienyl)iodocuprate is reduced by lithium naphthalenide to a highly reactive Cu(0) species which, upon successive treatment with a *t*-butyl ester of an ω-iodocarboxylic acid and either [C-11]- or [C-13]-iodomethane gives terminally labelled carboxylic acid esters,[137] such as [18-C-11]-linolenic acid.[138] The analogous process using lithium(2-thienyl)cyanocuprate and ethyl 8-iodooctanoate gave 9-[C-14]-nonanoic acid after hydrolysis, though the latter step required somewhat more

vigorous conditions than for the removal of the *t*-butyl group.[139] Lithium ([C-11]-methyl)(2-thienyl)cuprate.LiCN was used in the synthesis of ^{11}C-mesterolone (**79**) by [C-11]-methyl iodide in 31–50% radiochemical yield 35–50 min after EOB. This involved the use of [C-11]-methyl-lithium, which was prepared from the labelled methyl iodide by reaction with BuLi. In the same paper, [C-13]-labelled material was made from [C-13]-methyl iodide by similar chemistry.[140] A synthesis of (*R*)-α-amino-(6-[C-14]-methyl)-6,7-dimethyl-3-(phosphonomethyl)-quinolinepropanoic acid (**80**) relies upon the Ni(dppp)-induced coupling of the 6-bromoquinoline analogue with an organozinc reagent from [C-14]-methyl iodide.[141]



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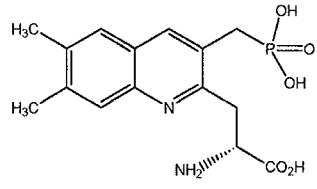


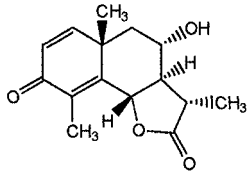
80

The alkylation of either diethyl malonate or ethyl acetoacetate to provide alkylated acetic acid systems has a venerable history. The alkylation of diethyl malonate is often preferred from the pragmatic observation that this can give only the desired carboxylic acid. However, recent studies of the preparation of 2-alkylated propanoic acids, in which appropriately alkylated esters of malonic acid or of acetoacetic acid are further alkylated by [C-11]-methyl iodide or [C-14]-methyl iodide, recommend the use of ethyl acetoacetate. The reasons for this preference are the milder conditions required for cleavage (conc. KOH, 5 min, 70°) and the better yields (50–70%) of the desired carboxylic acids, even though ketones are a minor by-product. Hydrolysis of the corresponding malonic ester and its partial decarboxylation requires more forcing conditions, and gives lower yields.[142]

Deuteriomethylation

N-Deuteriomethylation. [H-2(3)]-methylation by the use of appropriate alkylating agents has been reported. For example, base-catalysed transesterification using deuteriated methanol provided labelled ajmalicine, catharanthine, tabersonine, and yohimbine.[143] Labelled

creatinine was synthesized by methylation of guanidoacetate with *S*-adenosyl-[methyl-H-2(3)]-L-methionine (**4**) in the presence of rat liver guanidoacetate methyltransferase.[144] [H-2(3)]-methyl iodide similarly allowed the synthesis of labelled artemisinin (**81**) and arteether (**82**),[145] cefepime (**83**)[146] and methyl-3(5)pyrazoles.[147]



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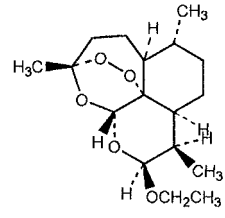

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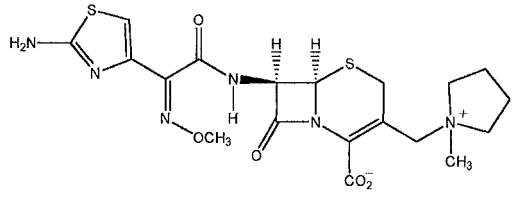

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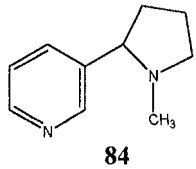
Racemic nornicotine reacts with [1-H-2(3)]-iodomethane, in the presence of *n*-BuLi at −70°C, providing racemic ([1-H-2(3)]methyl)nicotine (**84**) in high yield (91%).[148] The pyrrolidine ring may then be cleaved by ethyl chloroformate to give *E*-*N*-([1-H-2(3)]-methyl)-*N*-ethyloxycarbonyl-4-(3-pyridinyl)-3-buten-1-amine; in this reaction, elimination of HCl occurred during heating of the intermediate



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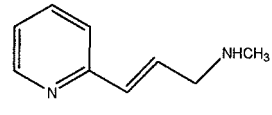
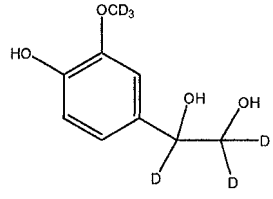


85

N-([1-H-2(3)]-methyl)-*N*-ethyloxycarbonyl-4-chloro-4-(3-pyridinyl)-butan-1-amine under low pressure (0.5 mm Hg). The last step of the synthesis, the removal of the *N*-carbamoyl group, was achieved via acidic hydrolysis with concentrated aqueous hydrochloric acid, and gave ([1-H-2(3)]-methyl)metanicotine (**85**; 82% overall yield; 97.6 atom% w.r.t. deuterium by mass spectrometry).

O-deuteriomethylation. The single-step synthesis of 4-hydroxy-3-([H-2(3)]methoxy)benzaldehyde ([H-2(3)]-vanillin) is reported from the interaction of [H-2(3)]-iodomethane with 3,4-dihydroxybenzaldehyde in strongly basic conditions.[149] This selective methylation may be compared with that shown in the earlier synthesis[150] of 1-(4-hydroxy-3-([H-2(3)]-methoxy)phenyl)-[1,2,2-H-2(3)]ethane-1,2-diol (**86**). Another early example is in the synthesis of 6,7-dihydro-10-trideuteriomethyl-6,8,8-trimethyl-8H-pyrano[3,2-g]-chromone-2-carboxylic acid.[151]



86

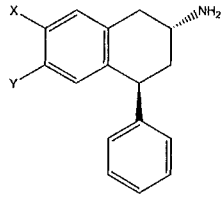
Tritiomethylation

N-tritiomethylation. [H-3(3)]-methyl iodide is often made from [H-3(3)]-methanol, itself obtained by the reduction of carbon dioxide. Tritium gas may be used to achieve this, but under fairly forcing conditions. Although the preparation of lithium aluminium tritide requires the intermediate formation of lithium tritide, itself obtained by the acid–base reaction of tritium gas with BuLi,[152] this method is reported[153] to provide methyl iodide containing the three isotopically labelled species [H-3(3)] : [H-3(2)] : [H-3(1)] in the ratio 87 : 7 : 6. Another synthesis of [H-3(3)]-methyl iodide uses the tritiolysis of 4-(trichloromethoxy)biphenyl followed by treatment with hydrogen iodide.[154] This method, which is equally as wasteful of the label, gives methyl iodide in which much more light hydrogen has been incorporated into the methyl group, the corresponding ratios now being 44 : 42 : 14. Tritiodehalogenation also provided [H-3(3)]-L-methionine through the hydrogenolysis of a trichloromethyl derivative of BOC-L-methionine.[153]

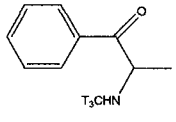
N-methylation is used to provide tritium labelling to a range of pharmaceuticals, including *N*,*N*-dimethyl-*S*(+)- and -*R*(−)-2-hydroxypropylamine, *S*-(−)- and *R*-(+)-2-(*N*,*N*-dimethylamino)propanol and *N*,*N*-dimethylpropynylamine,[155] *R*(−), *S*(+)-, and racemic (3,4-methylenedioxy)amphetamine (**49a**),[156] *trans*-1-phenyl-3-amino-1,2,3,4-tetrahydronaphthalene (**87**, X = Y = H)[157] and its 6-chloro-7-hydroxy

analogue (**87**; X = Cl, Y = OH),[158] JES-2316 (providing JES-1798)[159] and PF1022-219 (giving PF-1022A),[160] and routes to tritiated VUF-4576[161] and *N*-methyl-*N*-(chloroformyl)-*N*′-BOC-*p*-phenylene-diamine.[162]

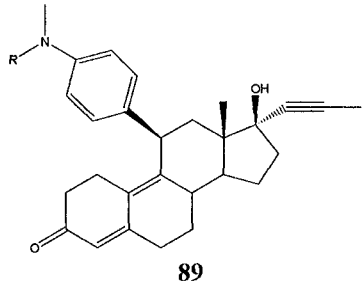
Methyl *N*2-(2,4-dimethoxybenzyl)-*N*(*G*)-(mesitylenesulfonyl)arginate may be alkylated with [H-3(3)]-methyl iodide and silver oxide. Transfer hydrogenation (4.4% HCO_2H in MeOH with Pt-black) removes the dimethoxybenzyl group, and saponification then give *N*(*G*)-mesitylene-



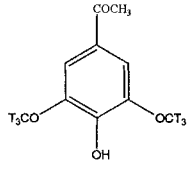
87



88



89



90

sulfonyl-[H-3]arginine in 30–38% yield from [H-3(3)]-methyl iodide.[163]

Tritiated methcathinone (2-([H-3(3)]methylamino)-1-phenylpropan-1-one, **88**) is also reported to be formed from the action of [H-3(3)]-methyl iodide upon cathinone in toluene/methanol, though the yield based upon methyl iodide is poor (4%) and the required chromatographic separation argues against an application to incorporate ^{11}C.[164] Likewise, desmethyl-RU486 (**89**; R = H) is alkylated by tritiated iodomethane to give ([H-3(3)]-methyl)-RU486 (**89**; R = ^3H_3C; specific activity, 85 Ci mmol^{-1}).[165]

O-tritiomethylation. Acetosyringone (**90**, 3,5-[H-3(6)]dimethoxy-4-hydroxyacetophenone) has been made using [H-3(3)]-methyl iodide under standard alkylation conditions.[153] The phenolic hydroxyl group was protected by isopropylation, and the acetyl group through the dimethyl

ketal. The Ph_2P^- anion, formed from Ph_2PH and BuLi in THF, dealkylated the –OMe functions but not the bulkier isopropoxyl system. Methylation ([H-3(3)]-methyl iodide, K_2CO_3, DMF) and deprotection ($TiCl_4$) then provided tritium-labelled acetosyringone.

Conclusions

The availability of deuterium- and tritium-labelled inorganic reagents (e.g. $LiAl^2H_4$) and hence of sources of carbon-labelled organic compounds, such as the methyl halides and methyl triflate, has encouraged the preparation of pharmaceutically active substances containing isotopically labelled methyl groups. The most popular methods involve nucleophilic displacement upon N, S, or O groups, although methylation upon carbon has been reported and Grignard or Barbier-type chemistry is also available. Reductive dehalogenation has been used to incorporate ^2H or ^3H into methyl substituents.

Conventional organic chemistry can be applied to the preparation of organic compounds containing stable or long-lived carbon or hydrogen isotopes, but the incorporation of ^{11}C into such compounds requires comparatively rapid methods of synthesis, isolation and purification to avoid extensive loss of the radio-label and, potentially, destruction through radiolysis.

The extension of these synthetic methods to the incorporation of larger radiolabelled alkyl groups rests upon the availability of the appropriate starting materials.

References

1. Vanderwalle T, Vandecasteele C. *J Label Cpd Radiopharm* 1982; **19**(11-1): 1376–1378.
2. Berger G, Prenant C, Sastre J, Comar D. *J Label Cpd Radiopharm* 1982; **19**(11-1): 1486–1487.
3. Berger G, Maziere M, Godot JM, Prenant C, Comar D. *J Label Cpd Radiopharm* 1981; **18**(11): 1649–1671.
4. Rossler K, Lattke H, Mathias C, Alshukri LM, Vogt M. *J Label Cpd Radiopharm* 1982; **19**(11-1): 1618–1619.
5. Långström B, Sjoberg S, Bergson G, Lundqvist H, Malmborg P, Stalnacke CG, Larsson B. *J Label Cpd Radiopharm* 1981; **18**(1–2): 17–19.

6. Wagner R, Stocklin G. *J Label Cpd Radiopharm* 1981; **18**(1–2): 189.
7. Långström B, Lundqvist H. *Int J Appl Radiat Int* 1976; **27**(7): 357–363.
8. Marazano C, Maziere M., Berger G, Comar D. *Int J Appl Radiat Int* 1977; **28**(1–2): 49–52.
9. Crouzel C, Långström B, Pike VW, Coenen HH. *Appl Radiat Isot* 1987; **38**: 601–603.
10. van Dort ME, Tluczek L. *J Label Cpd Radiopharm* 2000; **43**(6): 603–612.
11. Sandell J, Langer O, Larsen P, Dolle F, Vaufrey F, Demphel S, Crouzel C, Halldin C. *J Label Cpd Radiopharm* 2000; **43**(4): 331–338.
12. Hara T, Kosaka N, Shinoura N, Kondo T. *J Nucl Med* 1997; **38**(6): 842–847.
13. Halldin C, Farde L, Högberg T, Hall H, Sedvall G. *Appl Radiat Isot* 1990; **41**: 669–674.
14. Sarkadi E, Kovacs Z, Ando L, Szelecsenyi F. *Radiochim Acta* 1997; **76**(4): 197–200.
15. Sarkadi E, Kovacs Z, Horvath G, Lehikoinen P. *Radiochim Acta* 1998; **83**(1): 49–52.
16. De Vos F, Dumont F, Santens P, Slegers G, Dierckx RA, De Reuck J. *J Label Cpd Radiopharm* 2000; **43**(10): 989–996.
17. Schonbachler R, Ametamey SM, Schubiger PA. *J Label Cpd Radiopharm* 1999; **42**(5): 447–456.
18. Steel CJ, Prenant C, Shah F, Brown G, Henderson D, Brady F, Luthra SK, Pike VW. *J Nucl Med* 1998; **39**(5): 237p.
19. Mock BH, Mulholland GK, Vavrek MT. *Nucl Med Biol* 1999; **26**(4): 467–471.
20. Zessin J, Mading P, Krug H, Gommlich S, Jung B, Losel E, Dohn N, Fuchtner F, Steinbach J. *Wiss- Tech Ber Forschungszent Rossendorf* (FZR-270) 1999; 137–138; *Chem Abstr* 2000; **132**: 224186x.
21. Larsen P, Ulin J, Dahlstrom K, Jensen M. *Appl Radiat Isot* 1997; **48**: 153–157.
22. Hostetler ED, McCarthy TJ, Fallis S, Welch MJ, Katzenellenbogen JA. *J Org Chem* 1998; **63**(4): 1348–1351.
23. Sasaki M, Ikemoto M, Mutoh M. *Appl Radiat Isot* 2000; **52**(2): 199–204.
24. Harada N, Sato K, Tsukado H. JP 2000 128, 860; *Chem Abstr* 2000; **132**: 294009r.
25. Gueguen P, Morgat JL, Maziere M, Berger G, Comar D, Maman M. *J Label Cpd Radiopharm* 1982; **19**(2): 157–170.
26. Meyer GJ, Osterholz A, Hundeshagen H. *J Label Cpd Radiopharm* 1982; **19**(11-1): 1286–1287.
27. Hara T, Yuasa M. *Appl Radiat Isot* 1999; **50**(3): 531–533.

28. Jacobson GB, Markides KE, Långström B. *Acta Chem Scand* 1997; **51**(3, Suppl.): 418–425.
29. Stone-Elander SA, Elander N, Thorell JO, Solas G, Svennebrink J. *J Label Cpd Radiopharm* 1994; **34**(10): 949–960.
30. Krasikova R, Fedorova O, Korsakov M, Någren K, Maziere B, Halldin C. *J Label Cpd Radiopharm* 2000; **42**(6): 613–621.
31. Zessin J, Steinbach J. *Forschungszent Rossendorf* 1997; **FZR** (FZR-200): 196–198; *Chem Abstr* 1998; **128**(19): 230475z.
32. Zessin J, Steinbach J, Johannsen B. *J Label Cpd Radiopharm* 1999; **42**(8): 725–736.
33. Zessin J, Steinbach J. *J Label Cpd Radiopharm* 1998; **41**(7): 669–676.
34. Zessin J, Steinbach J. *Forschungszent Rossendorf* 1997; **FZR** (FZR-165): 169–172; *Chem Abstr* 1997; **127**: 50331v.
35. Långström B, Antoni G, Gullberg P, Halldin C. *J Label Cpd Radiopharm* 1984; **21**(11-1): 1207–1208.
36. Lu SJ, Li MI, Jeffrey AM. *J Label Cpd Radiopharm* 1989; **27**(8): 939–943.
37. Braun MP, Dean DC, Melillo DG. *J Label Cpd Radiopharm* 1999; **42**(5): 469–476.
38. Rhee SW, Ryan KJ, Tracy M, Kelson AB, Clizbe LA, Chang MH, Park JS, Roh JK, Kong JY, Yang JG, Kim WB, Ok KD. *J Label Cpd Radiopharm* 1997; **39**(9): 773–785.
39. Halldin C, Farde L, Högberg T, Hall H, Ström P, Ohlberger A, Solin O. *Nucl Med Biol* 1995; **18**: 871.
40. Halldin C, Farde L, Hoegberg T, Mohell N, Hall H, Suhara T, Karlsson P, Nakashima Y, Swahn C-G. *J Nucl Med* 1995; **36**(7): 1275–1281.
41. Patt JT, Spang JE, Westera G, Schubiger PA. *J Label Cpd Radiopharm* 2000; **43**(2): 127–136.
42. Sassaman MB, Panico M, Schmall B, Eckelman WC. *J Label Cpd Radiopharm* 1999; **42**(13): 1229–1233.
43. Maziere M, Godot J-M, Berger G, Prenant CH, Comar D. *J Radioanal Chem* 1980; **56**: 229–235.
44. de Vos F, Santeus P, Slegers G, Vermeirsch H, Dierckx RA, de Reuck J. *J Label Cpd Radiopharm* 2000; **43**: 595–601.
45. Wilson AA, Houle S. *J Label Cpd Radiopharm* 2000; **42**(12): 1277–1288.
46. Wilson AA, DaSilva JN, Houle S. *J Label Cpd Radiopharm* 1996; **38**(2): 149–154.
47. Jewitt DM. *Appl Radiat Isot* 1987; **38**: 601–603.
48. Holschbach M, Schuller M, Bender D, Roden W, Stöcklin G. *J Nucl Med* 1993; **34**(5): 68p.
49. Dolle F, Bottlaender M, Demphel S, Emond P, Fuseau C, Coulon C, Ottaviani M, Valette H, Loc'h C, Halldin C, Mauclaire L, Guilloteau D, Maziere B, Crouzel C. *J Label Cpd Radiopharm* 2000; **43**(10): 997–1004.

50. Någren K, Halldin C. *J Label Cpd Radiopharm* 1998; **41**(9): 831–841.
51. Någren K, Halldin C, Müller L, Swahn C-G, Lehikoinen P. *Nucl Med Biol* 1995; **22**(8): 965–970.
52. Lundkvist C, Halldin C, Swahn C-G, Ginovart N, Farde L. *Nucl Med Biol* 1999; **26**(4): 343–350.
53. Halldin C, Foged C, Chou Y-H, Karlsson P, Swahn C-G, Sandell J, Sedvall G, Farde L. *J Nucl Med* 1998; **39**(12): 2061–2068.
54. Kämäräinen E-L, Kyllönen T, Airaksinen A, Lundkvist C, Yu M, Någren K, Sandell J, Langer O, Vepsäläinen J, Hiltunen J, Bergström K, Lötjönen S, Jaakkola T, Halldin C. *J Label Cpd Radiopharm* 2000; **43**(12): 1235–1244.
55. Lundkvist C, Sandell J, Någren K, Pike VW, Halldin C. *J Label Cpd Radiopharm* 1998; **41**(6): 545–556.
56. Lundkvist C, Halldin C, Swahn C-G, Müller L, Ginovart N, Nakashima Y, Karlsson P, Neumeyer JL, Wang S, Milius RA, Farde L. *Nucl Med Biol* 1995; **22**(7): 905–913.
57. Langer O, Någren K, Dolle F, Lundkvist C, Sandell J, Swahn C-G, Vaufrey F, Crouzel C, Maziere B, Halldin C. *J Label Cpd Radiopharm* 1999; **42**(12): 1183–1193.
58. Matarrese M, Soloviev D, Moresco RM, Todde S, Simonelli P, Colombo D, Magni F, Carpinelli A, Fazio F, Kienle MG. *J Label Cpd Radiopharm* 2000; **43**: 359–374.
59. Zheng QH, Mulholland GK. *Nucl Med Biol* 1996; **23**: 981–986.
60. Snyder SE, Sherman PS, Desmond TJ, Frey KA, Kilbourn MR. *J Label Cpd Radiopharm* 1999; **42**(7): 641–652.
61. Alauddin MM, Fissekis JD, Conti PS. *Nucl Med Biol* 1997; **24**(8): 771–775.
62. Mosevich LK, Kuznetsova OF, Vasil'ev DA, Anishkov AA, Korsakov MV. *Radiochemistry (Moscow)* 1999; **41**(3): 273–280; *Chem Abstr* 1999; **131**: 299666s.
63. Långström B, Antoni G, Halldin C, Malmborg P, Någren K, Rimland A, Sjoberg S, Svard H, Bergson G. *J Label Cpd Radiopharm* 1984; **21**(11-1): 1200–1202.
64. Svard H, Någren K, Malmborg P, Sohn D, Sjoberg S, Långström B. *J Label Cpd Radiopharm* 1982; **19**(11-1): 1519–1520.
65. Diksic M, Jolly D. *J Label Cpd Radiopharm* 1984; **21**(11-1): 1199.
66. Angelini G, Carnevaletti F, Margonelli A, Corsi G, Ragni P, Fazio F, Todde S, Tinti O. *Appl Radiat Isot* 1999; **50**(2): 303–309.
67. Haradahira T, Sasaki S, Maeda M, Kobayashi K, Inoue O, Tomita U, Nishikawa T, Suzuki K. *J Label Cpd Radiopharm* 1998; **41**(9): 843–858.
68. Vandort ME, Kilbourn MR, Mangner TJ. *J Label Cpd Radiopharm* 1994; **34**(5): 447–452.

69. Lever JR, Kinter CM, Ravert HT, Musachio JL, Mathews WB, Dannals RF. *J Label Cpd Radiopharm* 1995; **36**(2): 137–145.
70. Dannals RF, Neumeyer JL, Milius RA, Ravert HT, Wilson AA,Wagner HN. *J Label Cpd Radiopharm* 1993; **33**(2): 147–152.
71. Någren K, Takahashi T, Lehikoinen P, Bergman J. *J Label Cpd Radiopharm* 1991; **29**(9): 1085–1089.
72. Barre L, Lasne MC, Charbonneau P. *J Label Cpd Radiopharm* 1995; **36**(8): 801–803.
73. Dolle F, Dolci L, Valette H, Bottlaender M, Fournier D, Fuseau C, Vaufrey F. Crouzel C. *J Label Cpd Radiopharm* 1996; **38**(12): 1099–1112.
74. Gee AD, Moldt P, Gjedde A. *J Label Cpd Radiopharm* 1997; **39**(12): 959–972.
75. Shiue C-Y, Pleus RC, Shiue GG, Rysavy JA, Sutherland JJ, Cornish KG, Young SD, Bylund DB. *Nucl Med Biol* 1998; **25**(2): 127–133.
76. Horti A, Ravert HT, Dannals RF, Wagner HN. *J Label Cpd Radiopharm* 1992; **31**(12): 1029–1036.
77. Ravert HT, Dannals RF, Wilson AA, Wagner HN. *J Label Cpd Radiopharm* 1992; **31**(5): 403–407.
78. Kassiou M, Mathews WB, Musachio JL, Ravert HT, Lambrecht RM, Dannals RF. *J Label Cpd Radiopharm* 1994; **34**(5): 431–437.
79. Noble GD, Dannals RF, Ravert HT, Wilson AA, Wagner HN. *J Label Cpd Radiopharm* 1992; **31**(2): 81–89.
80. Kothari PJ, Finn RD, Larson SM. *J Label Cpd Radiopharm* 1995; **36**(6): 521–528.
81. Burns HD, Lever JR, Dannals RF, Frost JJ, Wilson AA, Ravert HT, Subramanian B, Zemyan SE, Långström B, Wagner HN. *J Label Cpd Radiopharm* 1984; **21**(11-1): 1167–1169.
82. Foged C, Halldin C, Swahn C-G, Ginovart N, Karlsson P, Lundkvist C, Farde L. *Nucl Med Biol* 1998; **25**(5): 503–508.
83. Turton DR, Pike VW, Cartoon M, Widdowson DA. *J Label Cpd Radiopharm* 1984; **21**(11-1): 1209–1210.
84. Mulholland GK, Jung YW. *J Label Cpd Radiopharm* 1992; **31**(4): 253–259.
85. Ishiwata K, Noguchi J, Ishii S-I, Hatano K, Ito K, Nabeshima T, Senda M. *Nucl Med Biol* 1998; **25**(3): 195–202.
86. Haradahira T, Inoue O, Kobayashi K, Suzuki K. *Nucl Med Biol* 1998; **25**(3): 203–208.
87. Amokhtari M, Anderson K, Ibazizene M, Dhilly M, Dauphin F, Barre L. *Nucl Med Biol* 1998; **25**(6): 517–522.
88. Gillinge NM, Gee AD, Inoue O. *Appl Radiat Isot* 1999; **50**(4): 707–714.
89. Patt M, Gundisch D, Wullner U, Blocher A, Kovar K-A, Machulla H-J. *J Radioanal Nucl Chem* 1999; **240**(2): 535–540.

90. Dolle F, Valette H, Hinnon F, Fuseau C, Peglion J-L, Crouzel C. *Nucl Med Biol* 1998; **25**(4): 339–342.
91. Horti AG, Scheffel U, Kimes AS, Musachio JL, Ravard HT, Mathews WB, Zhan Y, Finley PA, London ED, Dannals RF. *J Med Chem* 1998; **41**(22): 4199–4206.
92. Ametamey S, Vollenweider FX, Patt J, Bourquin D, Hasler F, Beer HF, Schubiger PA. *J Label Cpd Radiopharm* 1998; **41**(7): 585–594.
93. Wilson AA, Inabo T, Fischer N, Dixon LM, Nobrega J, DaSilva JN, Houle S. *Nucl Med Biol* 1998; **25**(8): 769–776.
94. Wilson AA, Garcia A, Li J, DaSilva JN, Houle S. *J Label Cpd Radiopharm* 1999; **42**(7): 611–620.
95. Devos F, Slegers G. *J Label Cpd Radiopharm* 1994; **34**(7): 643–652.
96. Ding YS, Sugano Y, Fowler JS, Salata C. *J Label Cpd Radiopharm* 1994; **34**(10): 989–997.
97. Dannals RF, Ravert HT, Frost JJ, Wilson AA, Burns HD, Wagner HN. *J Label Cpd Radiopharm* 1984; **21**(11-1): 1170–1171.
98. Bergstrom M, Bonasera TA, Lu L, Bergstrom E, Backlin C, Juhlin C, Långström B. *J Nucl Med* 1998; **39**(6): 982–989.
99. Matarrese M, Soloviev DV, Moresco RM, Farri V, Simonelli P, Magni F, Colombo D, Todde S, Carpinelli A, Fazio F, Kienle MG. *Bioorg Chem* 1998; **26**(2): 91–102.
100. Nishiyama S, Harada N, Tsukada H. JP 2000 86, 632; *Chem Abstr* 2000; **132**: 236992v.
101. Johnstrom P, Fredriksson A, Thorell JO, Stone-Elander S. *J Label Cpd Radiopharm* 1998; **41**(7): 623–629.
102. Mading P, Steinbach J, Johannsen B. *J Label Cpd Radiopharm* 2000; **43**(6): 565–583.
103. Haradahira T, Suzuki K. *Nucl Med Biol* 1999; **26**(2): 245–247.
104. Wilson AA, DaSilva JN, Houle S. *J Label Cpd Radiopharm* 1994; **34**(8): 759–765.
105. Swahn C-G, Halldin C, Gunther I, Patt J, Ametamey S. *J Label Cpd Radiopharm* 1996; **38**(7): 675–685.
106. Vandersteene I, Audenaert K, Slegers G, Dierckx RA. *J Label Cpd Radiopharm* 1998; **41**(3): 171–180.
107. Holschbach M, Hamkens W, Roden W, Feinendegen LE. *J Label Cpd Radiopharm* 1991; **29**(5): 599–606.
108. Suehiro M, Wang TS, Yatabe T, VanHeertum RS, Mann JJ. *J Label Cpd Radiopharm* 1998; **41**(8): 725–730.
109. Suehiro M, Ravert HT, Dannals RF, Scheffel U, Wagner HN. *J Label Cpd Radiopharm* 1992; **31**(10): 841–848.
110. Huang YY, Mahmood K, Simpson NR, Mason NS, Mathis CA. *J Label Cpd Radiopharm* 1998; **41**(1): 9–17.

111. Maeding P, Noll S, Steinbach J, Spies H. *Forschungszent Rossendorf* 1997; **FZR** (FZR-200): 182–184; *Chem Abstr* 1998; **128**: 244224d.
112. Pascali C, Bogni A, Iwata R, Decise D, Crippa F, Bombardieri E. *J Label Cpd Radiopharm* 1999; **42**(8): 715–724.
113. Oh S-J, Choe YS, Kim YS, Choi Y, Kim SE, Lee KH, Ha H-J, Kim BT. *Bull Korean Chem Soc* 1998; **19**(9): 952–956; *Chem Abstr* 1998; **129**(24): 316514u.
114. Elbert T, Matucha M. *J Label Cpd Radiopharm* 1990; **28**(12): 1449–1453.
115. Fellows I, Carr RM, De Boeck N, Montgomery S, Waterhouse L, Sutherland DR. *J Label Cpd Radiopharm* 1998; **41**(12): 1127–1143.
116. Boukraa MS, Deruaz D, Bannier A, Desage M, Brazier JL. *J Label Cpd Radiopharm* 1995; **36**(8): 773–787.
117. Foged C, Hansen LB, Halldin C. *J Label Cpd Radiopharm* 1993; **33**(8): 747–757.
118. Irie T, Fukushi K, Nanba H, Iyo M, Ikota N, Nagatsuka S, Ueda T, Nishiura K, Takatoku K, Yamada I. WO 98 56, 763; *Chem Abstr* 1999; **130**: 81402k.
119. Taralp A, Kaplan H. *J Protein Chem* 1997; **16**(8): 183–193.
120. Luke GM, Swigor JE. *J Label Cpd Radiopharm* 1991; **29**(2): 193–199.
121. Takatori K, Nakajima Y, Hirose M, Kajiwara M. *Heterocycles* 1998; **47**(2): 717–724.
122. Martin A, Chassaing G, Vanhove A. *Isot Environ Health Stud* 1996; **32**(1): 15–19.
123. Jouko V, Heikki N, Esko P. *J Label Cpd Radiopharm* 1991; **29**(11): 1191–1196.
124. Thourel P, Vandais A, Noel JP, Beaucourt JP. *J Label Cpd Radiopharm* 1994; **34**(3): 275–279.
125. Arai H, Kasai M. *J Label Cpd Radiopharm* 1991; **29**(8): 902–908.
126. Barthes P, Duran H, Gorrichon L. *J Label Cpd Radiopharm* 1991; **29**(7): 797–804.
127. Beerli R, Borschberg HJ. *J Label Cpd Radiopharm* 1991; **29**(8): 957–961.
128. Taber DF, Meagley RP. *J Label Cpd Radiopharm* 1992; **31**(11): 849–851.
129. Landvatter SW. *J Label Cpd Radiopharm* 2000; **43**: 1321–1326.
130. McCarthy KE, Miller SA, Chenard BL, Butler TW, Dumont ML, Stemple JZ. *J Label Cpd Radiopharm* 1997; **39**(12): 973–985.
131. Raftery MJ, Gaskell SJ. *J Label Cpd Radiopharm* 1991; **29**(3): 313–318.
132. Chen H, Chan KK. *J Label Cpd Radiopharm* 1997; **39**(5): 369–377.
133. Suehiro M, Ravert HT, Wilson AA, Scheffel U, Dannals RF, Wagner HN. *J Label Cpd Radiopharm* 1992; **31**(2): 151–157.
134. Venkatachalam TK, Mzengeza S, Diksic M. *J Label Cpd Radiopharm* 1993; **33**(11): 1029–1038.
135. Fudala L, Lewin AH. *J Label Cpd Radiopharm* 1998; **41**(4): 261–266.

136. Ahmadian M, Bergström DE. *Nucleosides Nucleotides* 1998; **17**(9): 1183–1190.
137. Neu H, Kihlberg T, Långström B. *J Label Cpd Radiopharm* 1997; **39**(6): 509–524.
138. Neu H, Kihlberg T, Långström B. *J Label Cpd Radiopharm* 1997; **39**(7): 607–619.
139. Tetrick MA, Crenshaw TD, Benevenga NJ. *Anal Biochem* 1997; **248**(1): 1–6.
140. Neu H, Bonasera TA, Långström B. *J Label Cpd Radiopharm* 1998; **41**(3): 227–234.
141. Swahn BM, Andersson F, Pelcman B, Soderberg J, Claesson A. *J Label Cpd Radiopharm* 1997; **39**(3): 259–266.
142. Ogawa K, Sasaki M, Nozaki T. *Appl. Radiat Isot* 1997; **48**(5): 623–630.
143. Auriola S, Naaranlahti T, Lapinjoki SP. *J Label Cpd Radiopharm* 1991; **29**(1): 117–121.
144. Arcelloni C, Paroni R, Bonini PA, Magni F, Kienle MG. *J Label Cpd Radiopharm* 1992; **31**(7): 505–517.
145. Avery MA, Bonk JD, Mehrotra S. *J Label Cpd Radiopharm* 1996; **38**(3): 249–254.
146. Kamachi H, Okita T, Tsuno T, Naito T. *J Label Cpd Radiopharm* 1990; **28**(10): 1221–1227.
147. Iranzo GY, Elguero J. *J Label Cpd Radiopharm* 1990; **28**(8): 967–970.
148. Crooks PA, Ravard A, Byrd GD. *J Label Cpd Radiopharm* 1998; **41**(12): 1165–1171.
149. Schneider S, Rolando C. *J Label Cpd Radiopharm* 1992; **31**(6): 489–492.
150. Murray S, Baillie TA, Davies DS. *J Label Cpd Radiopharm* 1981; **18**(8): 1135–1140.
151. Minami N. *J Label Cpd Radiopharm* 1981; **18**(6): 823–827.
152. Liu Y-Y, Chen L-J. *J Label Cpd Radiopharm* 1996; **38**(1): 71–76.
153. Lee S, Morimoto H, Williams PG. *J Label Cpd Radiopharm* 1997; **39**(6): 461–470.
154. Soljoughian M, Morimoto H, Williams PG. *J Chem Soc Perkin Trans* 1990; **1**: 1803–1808.
155. Rajagopal S, Diksic M. *J Label Cpd Radiopharm* 1991; **29**(2): 231–236.
156. Hashimoto K, Hirai K, Goromaru T. *J Label Cpd Radiopharm* 1990; **28**(4): 465–469.
157. Wyrick SD, Booth RG, Myers AM, Kula NS, Baldessarini RJ, Mailman RB. *J Label Cpd Radiopharm* 1994; **34**(2): 131–134.
158. Wyrick SD, Booth RG, Myers AM, Kula NS, Baldessarini RJ. *J Label Cpd Radiopharm* 1992; **31**(11): 871–874.
159. Pleiss U, Turberg A, Harder A, Londershausen M, Jeschke P, Boheim G. *J Label Cpd Radiopharm* 1996; **38**(7): 651–659.

160. Pleiss U, Harder A, Turberg A, Londershausen M, Iinuma K, Mencke N, Jeschke P, Bonse G. *J Label Cpd Radiopharm* 1996; **38**(1): 61–69.
161. Caldirola P, Timmerman H. *J Label Cpd Radiopharm* 1992; **31**(12): 987–993.
162. Klotz P, Chatrenet B, Coppo M, Rousseau B, Goeldner M, Hirth C. *J Label Cpd Radiopharm* 1991; **29**(2): 149–155.
163. Landvatter SW. *J Label Cpd Radiopharm* 1993; **33**(9): 862–868.
164. Cozzi NV, Ruoho AE. *J Label Cpd Radiopharm* 1998; **41**(10): 927–933.
165. Mais DE, Chen LZ, Wagoner MA, Hayes JS, Wang MW. *J Label Cpd Radiopharm* 1995; **36**(12): 1199–1203.

